Department of Anesthesiology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

August 1, 2024

To whom it may concern,

Please find attached, documents for the study entitled," Pecto-Intercostal Fascial Plane Block for Enhanced Recovery After Cardiac Surgery, UW Madison: 2021-0111". This study has a ClinicalTrials.gov ID of NCT04928339. The forms have an institutional review board stamp from January 11, 2021, the most recent approval of the study.

Sincerely,

Jeremy Sullivan, PhD

University of Wisconsin-Madison
Consent to Participate in Research
And
Authorization to Use Protected Health Information for Research

Title of the Study: Pecto-Intercostal Fascial Plane Block for Enhanced Recovery After Cardiac Surgery

Lead Investigators: Patrick Meyer, MD (Phone: 608-263-8100)

Eric Simon, MD (Phone: 608-263-8100)

Where Lead Researchers work: University of Wisconsin- Madison, Department of Anesthesiology

UW HS-IRB # 2021-0111

Subject name **MR#**

Invitation

We invite you to take part in a research study about how the injection of numbing medication in a targeted area prior to surgery may improve pain control after surgery. We are inviting you because you are scheduled for a surgery where the block may be beneficial.

The purpose of this consent form is to give you the information you need to decide whether to be in the study. It also explains how health information will be used for this study and requests your authorization (permission) to use your health information. Ask questions about anything in this form that is not clear. If you want to talk to your family and friends before making your decision, you can. Once we have answered all your questions, you can decide if you want to be in the study. This process is called "informed consent."

What is the purpose of this study?

The purpose of this research study is to understand if the injection of numbing medication (bupivacaine) injected in the area by your pectoral and rib muscles may improve your pain control after surgery. This injection procedure is called a pecto-

IRB Approval Date: 4/8/2021
University of Wisconsin – Madison

intercostal fascial plane block. We are doing this research because there are studies indicating that this block may reduce pain experienced after different surgical procedures in the same area of the body and we want to study how it may affect recovery after a sternum incision. This research must be conducted to understand if the block can help improve pain control after surgery. Its use in this study is considered experimental.

This study is being conducted at University Hospital with funding from the UW Department of Anesthesiology. We plan to include 100 participants in this study.

What will happen in this study?

If you decide to participate in this research study you will be randomly assigned (like flipping a coin) to one of two groups. You will have an equal chance of being assigned to either of the two groups:

- Group 1: have the nerve block performed with bupivacaine injections.
- Group 2: have the nerve block performed with placebo (saline solution) injections

If you are in group 1, you will have the nerve block performed with bupivacaine and liposomal bupivacaine (shorter and longer acting numbing medications) on both sides of your chest before surgery. This will be performed after you are asleep under general anesthesia before they start your surgery. An ultrasound machine will be used to see the muscles of your chest and a bupivacaine mixture will be injected through a small needle in the correct location. We believe the numbing medication injected may help provide additional pain control after your surgery so you do not require as much pain medication. You will receive pain medication as needed after surgery to ensure you are comfortable, just as you would if you did not participate in the study.

If you are in group 2, you will have the nerve block performed with saline instead of any numbing medication. This will occur after you are asleep under general anesthesia before they begin your surgery. An ultrasound machine will be used to see the muscles of your chest and saline will be injected through a small needle in the correct location. We do not expect this group to have any benefit associated with your recovery after surgery. You will receive pain medication as needed after surgery to ensure you are comfortable, just as you would if you did not participate in the study.

You will not know which group you were randomly selected to. Your involvement in the study will not impact the anesthesia or surgery you receive in the operating room. After the operation you will receive standard care.

If you elect to participate in the study, you will be contacted by telephone approximately ninety days following your surgery and will be administered a brief pain survey over the

telephone. The purpose of this survey is to evaluate your pain, if any, and if you are using pain medications at this time following your operation. Following this phone call and survey, your participation in the study will be complete.

Protected health information (PHI) used in this study

Protected health information, also called PHI, is information about your physical or mental health that includes your name or other information that can identify you, like your date of birth or medical record number. From your medical records, health records, and/or billing records kept by the University of Wisconsin Hospital and Clinics we will collect the following:

- Age, date of birth, medical record number, height, weight, body mass index, gender, which procedure you are scheduled for, date of procedure, creatine levels, time it takes your blood to clot (an INR test), your platelet count, anticoagulation levels, your left ventricle ejection fraction, your right ventricular function, if you have scarring on your liver or have a liver disease diagnosis, any opioid use prior to surgery, your baseline pain score, pro ICU and hospital length of stay and clinical data from your surgery and recovery such as opioid use during and after the surgery, pain scores, time until rescue pain medication is used, time until bowel function returns, and your answers to a pain questionnaire 90 days after surgery.

How long will I be in this study?

You will receive the nerve block while you are asleep in your surgery. Your medical record will be used to follow the clinical data from your surgery and your recovery for 72 hours after your operation. You will then receive a follow up call and pain survey 90 days after your procedure. Following completion of this survey, your participation in the study will end.

The researchers may take you out of the study, even if you want to continue, if

- Any health change where the study is no longer in your best interest
- The study is stopped by the researchers.

Could taking part in the study help me?

You are not guaranteed to benefit directly from participating in this study. If you are randomized to receive the block with the bupivacaine injections you may have improved pain control after surgery. If you receive the block with the placebo injections, we do not expect you to have any direct benefit from the study. Even if the study does not help you directly, your participation in this research study may benefit other people in the future by helping us learn whether there is a clinical difference with the addition of the nerve block.

How is being in this study different from my regular health care?

We do not routinely administer this nerve block for this surgery. If you take part in the study you will have the nerve block performed with either the bupivacaine injections or saline injections while you are asleep under anesthesia just prior to your surgery. You will also be contacted via telephone at approximately 90 days following your operation for a survey. The remainder of your care will be unchanged.

Do I have to be in the study? What if I say "yes" now and change my mind later?

No, you do not have to be in this study. Taking part in research is voluntary. This means that you decide if you want to be in the study. If you decide now to take part, you can choose to leave the study at any time.

If you decide to be in the study, the researchers will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Let the researchers know if you choose to leave the study. If you decide not to take part in the study, or if you choose to leave the study, your choice will not affect any treatment relationship you have with healthcare providers at UW-Madison, UW Health or any affiliated organizations, or any services you receive from them. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are my other choices if I do not take part in this study?

If you decide not to take part in the study, you may undergo the surgery with regular care without the additional study procedures. Regular care would involve no nerve blocks or injections and no telephone survey at 90 days.

Are there any side effects or risks to me?

There are a few risks to this study that apply to all subjects. First, your study information could become known to someone who is not involved in performing or monitoring this study. A breach of confidentiality could result in damage to your reputation, but the chances of this happening are very small.

Nerve block injection risks (for both groups) include: bleeding, infection, nerve injury, injury to blood vessels, and the possibility your lung may collapse. These risks are very low and we will use an ultrasound machine during the injections to help reduce the chance of these risks occurring.

Potential adverse drug reactions for bupivacaine and liposomal bupivacaine include: Numbness around your lips, tingling in your face, ringing in your ear, restlessness, anxiety, dizziness, seizure, coma, slowing of your heart rate, changes to the rhythm of your heart, decreased heart function, low blood pressure, allergic reactions. The reactions that could affect your nerves/brain and/or your heart/blood pressure are very rare and tend to result in the event of an overdose, inappropriate injection of the medicine into a blood vessel or due to your body not breaking down the medication appropriately.

Specific to liposomal bupivacaine (10% or more): nausea, vomiting, constipation

Whenever an ultrasound is done, there is the chance of finding something unexpected. Unexpected findings can have clear clinical significance, or uncertain clinical significance. Clear clinical significance means that the ultrasound shows a problem that may be treatable and we generally know what the risks are of not treating the problem. Uncertain clinical significance means that the imaging shows something unusual in the spine, but we do not know if it might affect your health, and treatment may not be appropriate or possible. On this study, you will be informed of any findings of clear clinical significance that may be discovered during the imaging procedure, but you will not be informed if there are findings of uncertain clinical significance. In order to assist us in interpreting incidental findings in the ultrasound, we are also seeking your permission to review your medical records if you are or have been a patient at this hospital.

There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The ultrasound we are using in this research study is used for guidance for the purpose of performing a block and is not meant as a diagnosis tool. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

You may also choose to have your physician informed of any findings of clear clinical significance that we report to you by checking the box below. Please note, however, that if you choose to have your physician informed of findings of clinical significance, that report will likely be placed in your medical record. Please indicate your preference by checking the appropriate box:

____ Yes, please inform my doctor of findings of clinical significance

OR

____ No, please do not inform my doctor of findings of clinical significance

If you do wish us to report any findings to your physician, you must provide us with the name and location of your primary physician.

Name of primary physician_____
City or clinic_____

This study may also involve risks which are currently unforeseeable. We will inform you as soon as possible if we discover any information that may affect your health, welfare, or decision to be in this study.

Will being in this study cost me anything?

You or your insurance company will have to pay for all costs for medical care related to your surgery, including co-payments and deductibles. You will not incur any additional costs from participating in this research study. You will have to pay for any costs your insurance does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may have to pay, you should contact your insurance company.

Will I be paid for my participation?

You will not be paid for your participation in this study.

What happens if I am injured or get sick because of this study?

If you are injured or get sick because of this study, medical care is available to you through UW Health, your local provider, or emergency services, as it is to all sick or injured people.

- If it is an emergency, call 911 right away or go to the emergency room.
- For non-emergency medical problems, contact your surgery team or your primary care physician.
- Call the Lead Researchers, Patrick Meyer or Eric Simon at 608-263-8100 to report your sickness or injury.

Here are some things you need to know if you get sick or are injured because of this research:

- If the sickness or injury requires medical care, the costs for the care will be billed to you or your insurance, just like any other medical costs.
- Your health insurance company may or may not pay for this care.
- No other compensation (such as lost wages or damages) is usually available.
- UW-Madison and UW Health do not have a program to pay you if you get sick or are injured because of this study.

- By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. You keep your legal rights to seek payment for care required because of a sickness or injury resulting from this study.

HOW WILL MY PRIVACY BE PROTECTED AND WHO WILL USE MY HEALTH INFORMATION?

We have strict rules to protect your personal information and protected health information (PHI). We will limit who has access to your name, address, phone number, and other information that can identify you. We will also store this information securely. We may publish and present what we learn from this study, but none of this information will identify you directly without your permission.

However, we cannot promise complete confidentiality. Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. We may also have to tell appropriate authorities, such as child protective services or health care providers, if we learn during the study that you or others are at risk of harm (for example, due to child or elder abuse, or suicidal thoughts).

Authorizing the research team to use your PHI means that we can release it to the people or groups listed below for the purposes described in this form. Once your health information is released outside UW-Madison or UW Health it may not be protected by privacy laws and might be shared with others. Also, with appropriate institutional permissions and confidentiality protections, we might use information that we collect during this study for other research or share with other researchers without additional consent or authorization from you or your legally authorized representative.

The information collected from you during this study and from your medical records will be used by the researchers and research staff of the UW-Madison and its affiliates (UW Health) for this study. It may also be shared with others at the UW-Madison.

Others at UW-Madison and its affiliates who may need to use your health information in the course of this research:

- UW-Madison regulatory and research oversight boards and offices
- Research support services staff at the UW-Madison and its affiliates
- Personnel who schedule or perform medical tests or procedures, handle accounting and billing, or do other tasks related to the study.

Others outside of UW-Madison and its affiliates who may receive your health information in the course of this research:

- The U.S. Food and Drug Administration

People outside the UW-Madison and its affiliates who receive your health information may not be covered by privacy laws and may be able to share your health information with others without your permission.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will information from this study go in my medical record?

- Some of the information that we collect about you for this study will be put in your medical record. This includes information about the procedures performed in the hospital: We will record the associated drug administration, if applicable, as well as any unanticipated problems that result from your participation. Both you and your UW Health providers will be able to see these records.
- A UW Health medical record will be created for you if you do not already have one.

IS MY PERMISSION VOLUNTARY AND MAY I CHANGE MY MIND?

Your permission is voluntary. You do not have to sign this form and you may refuse to do so. If you refuse to sign this form, however, you cannot take part in this research study. You may completely withdraw from the study at any time. Tell the researchers if you'd like to withdraw by verbal communication to any member of the study team, or by letter as outlined below.

If you decide to be in the study, the researchers will tell you about new information or changes in the study that may affect your willingness to continue in the study.

If you decide not to participate in this study or if you stop while the study is underway, the health care you receive from the UW-Madison and its affiliates will not be affected in any way. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

HOW LONG WILL MY PERMISSION TO USE MY HEALTH INFORMATION LAST?

By signing this form you are giving permission for your health information to be used by and shared with the individuals or institutions described in this form. Unless you withdraw your permission in writing to stop the use of your health information, there is no end date for its use for this research study. You may withdraw your permission at

any time by writing to either person whose name is listed below:

Patrick Meyer, MD
600 Highland Avenue, B6/339 CSC
Madison WI 53792

Eric Simon, MD
600 Highland Avenue, B6/339 CSC
Madison WI 53792

Beginning on the date you withdraw your permission, no new information about you will be used. Any information that was shared before you withdrew your permission will continue to be used. If you withdraw your permission, you can no longer actively take part in this research study.

WHO SHOULD I CONTACT IF I HAVE QUESTIONS?

Please take as much time as you need to think over whether or not you wish to participate. If you have any questions about this study at any time, contact the Principal Investigators Patrick Meyer or Eric Simon at 608-263-8100.

If you are not satisfied with response of research team, have more questions, or want to speak with someone about your rights as a research participant, contact the UWHC Patient Relations Representative at 608-263-8009.

Authorization to participate in the research study and permission to use and/or disclose my health information:

I have read this Consent and Authorization form describing the research study procedures, risks and benefits and how my health information will be used.
I have had a chance to ask questions about the research study, including the use of my health information.
I have received answers to my questions.
I voluntarily agree to participate in this research study and permit the researcher to use my health information as described above.
I will receive a copy of this form.

_____
Printed Name of Research Participant

_____
Signature of Research Participant Date

_____
Signature of Person Obtaining Consent Date

****You will receive a copy of this form****

Pecto-Intercostal Fascial Plane Block for Enhanced Recovery After Cardiac Surgery

Protocol Number: IRB #2021-0111
Multiple-Investigator: Patrick Meyer, MD
Multiple-Investigator: Eric Simon, MD

Funding will be provided by the Department of Anesthesiology's Research and Development (R&D) Committee.

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	01/11/2021	v1	

Table of Contents

1.0 STATEMENT OF COMPLIANCE

1. I have read this protocol and agree to conduct this trial in accordance with Good Clinical Practice (GCP), all stipulations of the protocol, the Declaration of Helsinki, and applicable regulatory requirements as stated by my human subjects testing oversight body [e.g., independent ethics committee (IEC) or institutional review board (IRB)].

2. I will personally conduct or supervise the described investigation(s). This includes informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.

3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

4. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Name	**Signature**	**Date**
Principal Investigator		
Name of Principal Investigator (printed or typed)		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAM-ICU	Confusion Assessment Method for the ICU
CPOT	Critical Care Pain Observation Tool
CRF	Case Report Form
CTMS	Clinical Trial Management Software
DOS	Day of Surgery
DSMB	Data & Safety Monitoring Board
DSMC	Data & Safety Monitoring Committee
FDA	Food and Drug Administration
eCRF	Electronic Case Report Forms
ERAS	Enhanced Recovery After Surgery
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IMA	Internal Mammary Artery
INR	International Normalized Ratio
IRB	Institutional Review Board
MME	Morphine Milligram Equivalents
NIH	National Institutes of Health
NRS	Numeric Rating Scale
OHRP	Office for Human Research Protections
OnCore	Online Collaborative Research Environment
PACU	Post-Anesthesia Care Unit
PHI	Protected Health Information
PI	Principal Investigator
PIFB	Pecto-Intercostal Fascial Plane Block
POD	Postoperative Day
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SOC	Standard of Care
TTP	Transversus Thoracic Plane
UP	Unanticipated Problem
X	Applies to Research Only

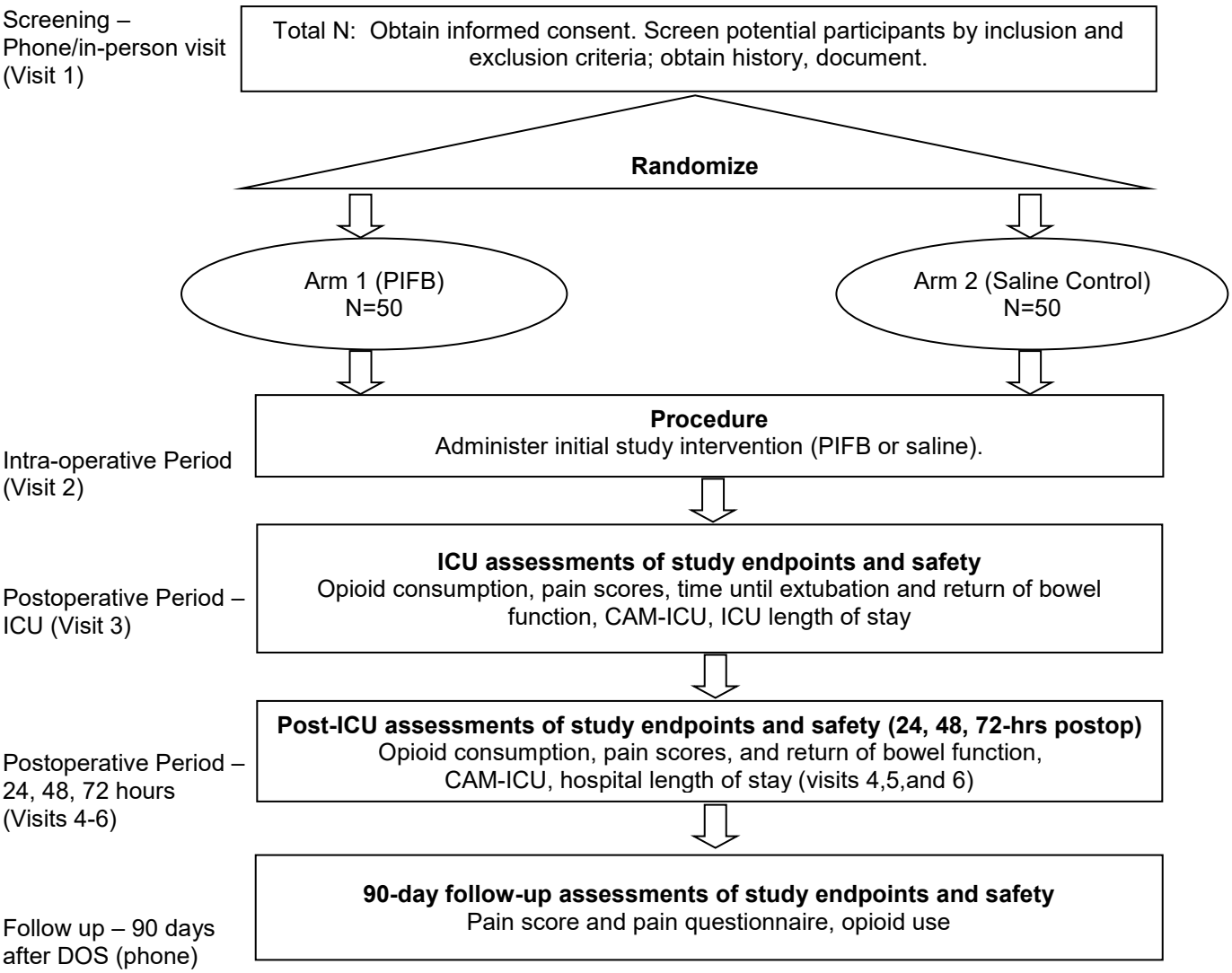
3.0 STUDY SUMMARY

3.1 Synopsis

Full Title	Pecto-Intercostal Fascial Plane Block for Enhanced Recovery After Cardiac Surgery
Short Title	PIFB and Recovery After Cardiac Surgery
Protocol Number	HS IRB 2021-0111
ClinicalTrials.gov Identifier & Summary	Pending This study is being done to see if bilateral pecto-intercostal fascial plane blocks with a mixture of liposomal and standard bupivacaine decrease pain and opioid requirements in patients undergoing cardiac surgery via median sternotomy compared to controls (sham blocks with saline).
Number of Site(s)	1
Main Inclusion Criteria	• The patient is 18-80 years old • The patient's ideal body weight (IBW) is >50kg • The patient is planned to undergo elective coronary artery bypass graft or single valve repair/replacement surgery via median sternotomy
Main Exclusion Criteria	• The patient has a preoperative coagulopathy (INR >1.4, platelets <100,000) or ongoing anticoagulation or anti-platelet therapy (except aspirin 81mg) • The patient has an allergy or sensitivity to amide-type local anesthetics, dexmedetomidine or ketamine • The patient has severe left ventricle dysfunction (defined quantitatively as an ejection fraction of less than or equal to 35%) or right ventricle dysfunction (defined qualitatively as "severe") • The patient uses chronic opioids (meaning at the time of the preoperative screening evaluation by the study team, the patient is prescribed and taking any opioid pain medication)
Objective(s)	<u>Primary Objective</u> • To evaluate postoperative opioid requirement within 72 hours in patients who received local anesthetics via PIFB compared to those control patients who received saline. <u>Secondary Objectives</u> • To evaluate intraoperative opioid consumption in patients who received local anesthetics via PIFB compared to those control patients who received saline. • To evaluate intensity of postoperative pain in patients who received local anesthetics via PIFB compared to those control patients who received saline. • To evaluate duration of mechanical ventilation in patients who received local anesthetics via PIFB compared to those control patients who received saline. • To evaluate return of bowel function in patients who received local anesthetics via PIFB compared to those control patients who received saline. • To evaluate postoperative delirium in patients who received local anesthetics via PIFB compared to those control patients who received saline. • To evaluate length of hospital stay in patients who received local anesthetics via PIFB compared to those control patients who received saline.

	• To evaluate chronic opioid use at 90 days postoperatively in patients who received local anesthetics via PIFB compared to those control patients who received saline.
Endpoints	Primary Endpoint • Total daily opioid consumption during the initial 72 hours postoperatively will be measured in morphine equivalents and compared between groups. Secondary Endpoints • Total intraoperative opioid consumption will be measured in morphine equivalents and compared between groups. • Pain will be assessed, according to standard of care, every 4 hours using the 11-point Numerical Rating Scale (NRS), beginning at time 0 (arrival to ICU). Each patient's pain scores within discrete 8-hour time intervals will be averaged, and the median pain scores during each time interval will be compared between the intervention and control groups. Pain at 90 days postoperative will be surveyed by phone. • Duration of mechanical ventilation will be measured by hours of mechanical ventilation after admission to the ICU. • Return of bowel function will be measured in the number of postoperative days until the first bowel movement. • Postoperative delirium will be measured according to standard of care by utilizing the Confusion Assessment Method for the ICU (CAM-ICU) assessment every 8-12 hours. • Intensive care unit length of stay will be measured by the number of hours that the patient is in the ICU before an order is placed for transfer to a lower level of care. • Duration of hospital stay will be measured by the number of post-operative days until the patient is discharged. • Patient use of opioids at 90 days will be obtained by phone call.
Study Design	This study is a prospective, single-center, randomized, double-blind, controlled trial to evaluate whether bilateral pecto-intercostal fascial plane blocks with liposomal and standard bupivacaine decrease pain and opioid requirements in patients undergoing cardiac surgery via median sternotomy compared to controls (sham blocks with saline).
Study Intervention	The patients will be randomized to receive bilateral PIFB with a mixture of standard and liposomal bupivacaine or bilateral PIFB with saline only. Recovery characteristics, including opioid consumption, pain scores, duration of mechanical ventilation, ICU length of stay, hospital length of stay, side effects, and chronic opioid use will be evaluated.
Total Number of Subjects	A total of 100 subjects will be recruited.
Statistical Methodology	Data analysis will be performed on an intent-to-treat basis based upon assignment to a study arm. Continuous data will be compared using student T-test or Wilcoxon-rank sum testing as appropriate. Categorical data will be compared using Chi-square or Fisher exact testing as appropriate. The data will be presented graphically where possible using scatter plots, profile plots, or histograms. For all tests, statistical significance will be defined as a p-value less than 0.05.
Estimated Subject Duration	The duration of the study for each subject is approximately 100 days.
Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 3 months with the total expected duration of the trial to be 24 months.

3.2 Schematic of Study Design



4.0 KEY ROLES

The following is a list of all key personnel and roles:

Multiple- Investigator	Patrick Meyer, MD Title: Assistant Professor Department of Anesthesiology University of Wisconsin-Madison UW School of Medicine and Public Health 600 Highland Avenue B6/319 CSC Madison, WI 53792-3272 (608)263-8100 psmeyer@wisc.edu
Multiple-Investigator	Eric R. Simon, MD Assistant Professor Department of Anesthesiology University of Wisconsin-Madison UW School of Medicine and Public Health 600 Highland Avenue B6/319 CSC Madison, WI 53792-3272 (608) 263-8100 esimon2@wisc.edu
Co-Investigator	Amy Fiedler, MD Assistant Professor Division of Cardiothoracic Surgery Department of Surgery University of Wisconsin-Madison UW School of Medicine and Public Health 600 Highland Ave Madison, WI 53792 (608) 262-3858 fiedler@surgery.wisc.edu
Participating Site(s)	University of Wisconsin-Madison UW School of Medicine and Public Health
Biostatistician	Bryan Krause, PhD Scientist, Biostatistician University of WI-Madison 600 Highland Ave, B6/319 Madison WI, 53792 bmkrause@wisc.edu.

5.0 INTRODUCTION

5.1 Background

Pain after cardiac surgery via median sternotomy occurs as a direct result of surgical manipulation and tissue trauma. Acute pain is typically an inflammatory response and may be related to the surgical incision, pericardiotomy, retraction, suturing, and/or chest tube placement, among other causes. Acute pain after cardiac surgery has historically been treated with intravenous opioids, however significant side effects may limit their use and efficacy. A subset of patients experience severe acute postoperative pain, which may increase length of stay, morbidity, mortality, and healthcare costs[1]. In addition, 30-50% of patients report chronic pain (lasting at least 2 months) after coronary bypass surgery[2], and the greatest predictor of chronic post-surgical pain is poorly controlled acute postoperative pain[2].

Over the past decade, with the emergence of enhanced recovery after surgery (ERAS) for cardiac surgery programs, cardiac anesthesiologists have been exploring unique options for maintenance of anesthesia and management of postoperative pain in place of high-dose opioids. Neuraxial anesthetic techniques have been used and studied extensively in this context, and while they appear safe and may even improve outcomes[4-6], persistent concern over the rare, yet devastating, risk of spinal or epidural hematoma during full heparinization has limited their use in cardiac surgery. In addition, paravertebral blocks have shown comparable analgesic effects after cardiac surgery compared to thoracic epidural blockade[7], however similar concerns over epidural hematoma exist.

The anteromedial chest wall, including the sternum, is innervated by the anterior cutaneous branches of the intercostal nerves. One option to target these nerves is the transversus thoracic plane (TTP) block, described by Ueshima et al, where local anesthetic is injected in the fascial plane between the transversus thoracic and internal intercostal muscles just lateral to the sternum[8]. However, the internal mammary artery (IMA) is located in the same plane, which could lead to devastating complications if this block is used for coronary bypass surgery involving the IMA.

The pecto-intercostal fascial plane block (PIFB) aims to block the anterior cutaneous branches of the intercostal nerves as they ascend in the parasternal region between the pectoralis major and external intercostal muscles. This block is superficial to the TTP and therefore should decrease the risk of injury to the IMA as well as the risk of pneumothorax. This block has been described by several different names in the literature, including the subpectoral interfascial plane block, the parasternal intercostal plane block, and the anterior thoracic medial block. Case reports and case series have demonstrated success in using this fascial plane block for acute post-sternotomy pain[9-10], sternal fractures or anterior rib fractures[11-14], and as an adjunct for coverage of medial breast procedures[15-18]. Two recently published randomized controlled trials have supported this block as safe and effective for reducing visual analog scale pain scores[19] and postoperative opioid requirements using standard bupivacaine injection within this fascial plane[20].

In 2011, the Food and Drug Administration (FDA) announced the approval of Exparel© liposomal bupivacaine formulation for surgical site infiltration and field blocks. It has been marketed for local nerve infiltration, hemorrhoidectomy, bunionectomy and fascial plane blocks. In 2018, the FDA expanded its indication to include interscalene brachial plexus blocks following further evidence of its efficacy and safety. One downside of single shot peripheral nerve blockade is the duration of analgesia can be relatively short lived. Exparel© uses the multivesicular liposomal formulation of bupivacaine to deliver an extended-release effect of local anesthetic. This extended-release action may offer the benefit of long-lasting opioid sparing effects of regional analgesia without the need for perineural catheters or repeat single-shot injections, which may be time-consuming, increase wound infection risk, and place the patient at risk of requiring repeat procedures. To that end, the use of liposomal bupivacaine in fascial plane blocks for colorectal surgery ERAS protocols has found advantages over single-shot techniques with standard bupivacaine[21]

and similar efficacy with less opioid use compared to a catheter/epidural-based analgesic approach[22]. The use of liposomal bupivacaine for cardiac surgery and median sternotomy has been limited with mixed results to date[23-24], with no studies to our knowledge evaluating its use in the PIFB.

This study aims to evaluate the efficacy of bilateral pecto-intercostal fascial plane blocks with liposomal bupivacaine in the setting of a multimodal perioperative analgesic regimen in elective cardiac surgery patients requiring median sternotomy.

5.2 Rationale

Thousands of heart surgeries are performed every day in the United States[25]. Unattenuated perioperative pain has been shown to contribute to increased morbidity, mortality, length of stay, and healthcare costs. Practice guidelines from the American Society of Regional Anesthesiologists recommend pre-incision techniques to reduce perioperative pain[26], however in cardiac surgery, there are no commonly used techniques to follow this recommendation. The PIFB is a newly described fascial plane block and existing literature supports the safety and efficacy of the PIFB in cardiac surgery patients. However, there are no randomized controlled trials evaluating this technique with a long-acting depot local anesthetic.

The purpose of this study is to determine whether bilateral pecto-intercostal fascial plane blocks with liposomal bupivacaine decrease pain and opioid requirements in patients undergoing cardiac surgery via median sternotomy compared to controls (sham blocks with saline). Our primary hypothesis is that patients receiving effective regional anesthesia with liposomal bupivacaine via PIFB will demonstrate a clinically significant (25%) reduction in total daily opioid consumption through 72 hours postoperatively compared to patients receiving standard of care without effective regional anesthesia (saline only via PIFB).

6.0 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate postoperative opioid requirement within 72 hours in patients who received local anesthetics via PIFB compared to those control patients who received saline.	Total opioid consumption during the initial 72 hours postoperatively will be measured in morphine equivalents and compared between groups.
Secondary	
• To evaluate intraoperative opioid consumption in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Total intraoperative opioid consumption will be measured in morphine equivalents and compared between groups.
• To evaluate intensity of postoperative pain in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Pain will be assessed, according to standard of care, every 4 hours using the 11-point Numerical Rating Scale (NRS), beginning at time 0 (arrival to ICU). Each patient's pain scores within each postoperative day will be averaged, and the mean pain scores during each day and throughout the first 72 hours will be compared between the intervention and control groups. Maximum pain scores will also be compared between groups. Pain

	at 90 days postoperative will be surveyed by phone.
• To evaluate daily postoperative opioid consumption within 72 hours in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Daily opioid consumption during the initial 72 hours postoperatively will be measured in morphine equivalents and compared between groups.
• To evaluate duration of mechanical ventilation in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Duration of mechanical ventilation will be measured by hours of mechanical ventilation after admission to the ICU.
• To evaluate return of bowel function in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Return of bowel function will be measured in the number of postoperative days until the first bowel movement.
• To evaluate postoperative delirium in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Postoperative delirium will be measured according to standard of care by utilizing the Confusion Assessment Method for the ICU (CAM-ICU) assessment every 8-12 hours.
• To evaluate ICU length of stay in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Duration of ICU stay will be measured by the number of hours that the patient is in the ICU until an order is placed for transfer to a lower level of care.
• To evaluate length of hospital stay in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Duration of hospital stay will be measured by the number of post-operative days until the patient is discharged.
• To evaluate chronic opioid use in patients who received local anesthetics via PIFB compared to those control patients who received saline.	• Patient use of opioids at 90 days will be obtained by phone call.

7.0 STUDY DESIGN

This study is a prospective, single-center, randomized, double-blind, controlled trial in which 100 patients will be enrolled at the University of Wisconsin Hospitals and Clinics. The patients must satisfy the inclusion and exclusion criteria below. The patients will be randomized to receive bilateral PIFB with liposomal bupivacaine or bilateral PIFB with saline only. Recovery characteristics, including opioid consumption, pain scores, duration of mechanical ventilation, ICU length of stay, hospital length of stay, side effects, and chronic opioid use will be evaluated.

8.0 SUBJECT SELECTION

8.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

1. The patient provides consent to participate in study.
2. The patient is 18-80 years old.
3. The patient's ideal body weight (IBW) is >50kg.
4. The patient is planned to undergo coronary artery bypass graft or single valve repair/replacement surgery via median sternotomy.
5. The patient is undergoing an elective procedure.

8.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. The patient is unable or unwilling to give consent.
2. The patient is non-English speaking.
3. The patient is known or believed to be pregnant or is currently breastfeeding.
4. The patient is a prisoner.
5. The patient is clinically unstable per discretion of the Investigator.
6. The patient requires urgent/emergent surgery.
7. The patient has a history of previous sternotomy.
8. Preoperative coagulopathy (INR >1.4, platelets <100,000) or ongoing anticoagulation or anti-platelet therapy (except aspirin 81mg).
9. The patient has an allergy or sensitivity to amide-type local anesthetics, dexmedetomidine or ketamine.
10. The patient has decompensated heart failure.
11. The patient has severe left ventricle dysfunction (defined quantitatively as an ejection fraction of less than or equal to 35%) or right ventricle dysfunction (defined qualitatively as "severe")
12. The patient has a diagnosis of cirrhosis or end-stage liver disease
13. The patient requires the use of mechanical circulatory support pre-operatively.
14. The patient uses chronic opioids (meaning at the time of the preoperative screening evaluation by the study team, the patient is prescribed and taking any opioid pain medication).

8.3 Vulnerable Populations

Prisoners

Due to the complexity of state and federal requirements governing the participation of prisoners in research, patients who are prisoners will not be considered for participation in this trial. In the unlikely event that a subject becomes a prisoner while participating in this trial, study procedures will stop and the subject will be returned to the clinical mode used prior to the intervention period or, if desired, an alternative mode requested by the clinical care team.

Pregnancy

Patients who are known to be pregnant will be excluded from participation.

8.4 Subject Identification

A member of the research team will review the surgery schedule at least one week in advance and identify patients who appear to be candidates for the study. The study team will work with the perioperative care team (including the assigned anesthesia staff and surgeon) to confirm eligibility criteria and potential participation. All protected health information used during the screening process of a potential subject will be the minimum necessary for the conduct of this study. Any protected health information recorded for

screening will be destroyed for ineligible patients once they are deemed ineligible by a study team member aside from the reason for exclusion. Any protected health information recorded for an eligible patient who declines study participation and is not enrolled in the study will immediately be destroyed.

8.5 Subject Recruitment and Informed Consent

When potential participants are identified and approved by the teams involved, a member of the study team will call the patient prior to the day of surgery and determine their interest in participating. On the day of surgery, potential participants will proceed through the usual preoperative process. A member of the study team will meet with the patients the morning of surgery. In order to ensure the candidate's privacy and confidentiality, the cubicle's curtain or room door will be closed. In a tone of voice insufficient for others to overhear the conversation and in the presence of only those immediately accompanying the patient and those who are directly involved with the patient's care, the candidate's eligibility, the study purpose, procedures, risks, benefits and alternatives will then be discussed. The written information about the study provided to the candidate at the time of their check-in will be reviewed and they will be instructed to take as much time as needed to consider their participation. Any questions that the candidate may have will be answered. Undue coercion will be prevented by stressing that the potential subject does not have to agree to participation and that the future care of the potential subject will not change regardless of the decision to participate. If the candidate has no further questions and would like to participate, they will be asked to sign the written informed consent document. The research subject will be given a copy of the signed and dated informed consent form. The original signed informed consent form is kept in a locked office in the Department of Anesthesiology.

8.6 Enrollment

A research subject will be defined as "enrolled" in the study when they meet the following criteria:

- The subject has been consented by study staff and has agreed to participate.
- The subject and study staff have completed all screening documentation.
- The PI has verified that the subject meets all of the inclusion criteria.
- The PI has verified that subject meets none of the exclusion criteria.
- The subject has been assigned to the protocol by study staff.
- The subject has been randomized.
- The subject has received the study intervention.

8.7 Early Termination and Withdrawal

At any point prior to or during the intervention period, the patient's clinical care team or a study physician may decide that the subject should be withdrawn from the study. In addition, at any point, a patient may elect to withdraw themselves from the study. If a patient is withdrawn from the study for any reason, the patient will then be followed according to standard of care follow-up. In the event that a subject is withdrawn from the study prematurely, the reason for withdrawal will be documented on a case report form.

9.0 PROCEDURAL INTERVENTION

9.1 Study Procedural Intervention(s) Description

The intervention portion of this study is the randomized assignment (1:1) to receive 25mL of saline or 15mL of 0.25% bupivacaine mixed with 10mL of liposomal bupivacaine (133mg) as a single-shot injection into the pecto-intercostal fascial plane bilaterally. All studied volumes are well within the acceptable range for pecto-intercostal nerve blocks described previously. All patients will be treated intraoperatively according to our institutional enhanced recovery after surgery for cardiac patients, including the use of dexmedetomidine and ketamine infusions with as-needed fentanyl intravenous dosing.

9.2 Method for Assigning to Treatment Groups

After consent is obtained, participants will be randomized to an intervention group. Randomization will be accomplished using an online service (www.randomizer.org) and prefilling sealed envelopes determining each subject's intervention group. Randomization will occur immediately prior to the intervention. All subjects will receive the standard of anesthesia care appropriate for their surgery or procedure as determined by the primary anesthesia team caring for the subject, regardless of randomization group. Each study subject as well as the OR anesthesia team, cardiac surgery team, cardiothoracic ICU team, and nursing staff caring for the patient will be blinded to the study drug the patient received. However, the anesthesia provider performing the block (separate from the provider caring for the patient in the operating room) will not be blinded to the study drug injected and will have access to all monitors deemed appropriate by the primary team caring for the subject. In order to maintain blinding during the procedure, the medication syringe will be covered by a towel after being drawn up and during injection to prevent the intraoperative teams from visualizing the contents being injected. The ultrasound will also be turned such that only the anesthesiologist performing the procedure can see, as Exparel has a distinct sonographic appearance on injection. Specific individuals who were involved in the block placement will not perform any follow-up assessments or evaluations of the study patients for the remainder of the study.

9.3 Unblinding Procedures

To minimize the safety risk associated with blinding, the anesthesiologist performing the block will be available to be contacted by other caregivers for unblinding in the situation where that becomes necessary for patient safety. The anesthesiologists, surgeons, intensivists and nursing staff will be aware that the patient is enrolled in a study and may have received bupivacaine with liposomal bupivacaine injections.

10.0 STUDY CALENDAR, MEASUREMENTS, AND ACTIVITIES

10.1 Study Calendar

	Screening Visit 1 Phone/ inperson visit	Procedure Visit 2	ICU Visit 3	24-hours Post-op Visit 4	48-hours Post-Op Visit 5	72-hours Post-op Visit 6	3 Months or 90 days after DOS (Phone)
Window	Up to 60 days before surgery	Morning of Surgery	Following surgical procedure	24 hours post-op +/- 6 hours	48 hours post-op +/- 6 hours	72 hours post-op +/- 6 hours	
Screening	X						
Eligibility	X	X					

Informed Consent	X	X					
Demographics	X						
Medical History	SOC						
Randomization and Intervention: Pecto-Intercostal Fascial Plane Blocks vs Sham (control)		X					
Electronic Data Collection (EDC)		X	X	X	X	X	
Brief Pain Inventory Form							X
Concomitant Medications[1]		SOC	X	X	X	X	X
Adverse Events		SOC		SOC			

[1] All medications taken for analgesia at home regularly, prior to arrival on the day of surgery, and perioperatively (until 72 hours postoperatively) will be recorded.
[2]. EDC will all capture the opioid intake, pain measuresurement and all other relevant study information that is not capture during the study procedures.

10.2 Study Measurements

10.2.1 Preoperative Period - Screening (Visit 1)

- Age
- Sex
- Height
- Weight
- Body mass index
- Date of surgery
- Procedure
- Indication for procedure
- Baseline creatinine

- Baseline INR
- Baseline platelet count
- Preoperative anticoagulation
- Baseline left ventricle ejection fraction
- Baseline qualitative right ventricular function
- Presence of cirrhosis or end-stage liver disease diagnosis
- Presence of preoperative opioid use
- Baseline pain score (Numeric rating scale [NRS])

10.2.2 Intra-operative Period (Visit 2)

- Surgery length
- Intraoperative opioid consumption
- ASA Status

10.2.3 Postoperative Period – ICU (Visit 3)

- Opioid consumption
- Pain scores (Critical Care Pain Observation Tool [CPOT], numeric rating scale [NRS]) q 4 hours
- Time until first rescue opioid analgesia
- Time until extubation
- Time until return of bowel function
- CAM-ICU q 8-12 hours
- ICU length of stay

10.2.4 Postoperative Period - 24 hours (Visit 4)

- Opioid consumption
- Pain scores (CPOT, NRS) q 4 hours
- Time until first rescue opioid analgesia
- Time until return of bowel function, recorded as time to first documented bowel movement
- CAM-ICU q 8-12 hours

10.2.5 Postoperative Period - 48 hours (Visit 5)

- Opioid consumption
- Pain scores (CPOT, NRS) q 4 hours
- Time until first rescue opioid analgesia
- Time until return of bowel function
- CAM-ICU q 8-12 hours

10.2.6 Postoperative Period - 72 hours (Visit 6)

- Opioid consumption
- Pain scores (CPOT, NRS) q 4 hours
- Time until first rescue opioid analgesia
- Time until return of bowel function
- CAM-ICU q 8-12 hours

- Hospital length of stay

10.2.7 Follow Up - 90 days after DOS (phone)

- Standardized pain questionnaire (Brief Pain Inventory Short Form)

Study Activities

1. Surgery clinic education form explaining the study will be provided to the patient.
2. Anesthesia schedule will be screened by a member of the research team at least one week in advance to identify prospective study participants.
3. One of the study team members will call the patient prior to the day of surgery, confirm eligibility to participate, explain the study, review the study materials and obtain verbal consent from patient prior to the DOS.
4. Prospective patients will be added to Anesthesia Block List with a note about the study after written consent is obtained from the patient.
5. On the day of surgery, the patient will proceed through the usual preoperative process. A member of the study team will meet the patient, evaluate the patient for interval changes in their health, and obtain written informed consent to participate in the study.
6. Randomization will occur the morning of surgery. The patient will be randomized to receive 15mL of 0.25% bupivacaine with 10mL of liposomal bupivacaine bilaterally vs 25mL saline bilaterally within the pecto-intercostal fascial plane.
7. The block team will perform ultrasound-guided bilateral single-shot PIFBs with 0.25% bupivacaine plus liposomal bupivacaine versus saline after induction of general anesthesia in the operating room.
8. The patient, in-room anesthesia team, surgical team, and ICU team will be blinded to randomization status. The block team will not be blinded given the need to draw-up medications immediately prior to block placement and the distinct sonographic appearance of liposomal bupivacaine. The medication syringe will be covered by a towel after being drawn up and during injection to prevent blinded parties from visualizing the contents being injected. The ultrasound will also be turned such that only the anesthesiologist performing the procedure can see.
9. All patients participating in the study will receive wrist bands indicating the possible use of liposomal bupivacaine to avoid additional local anesthetic or regional intervention for at least 96 hours following the nerve block or sham procedure.
10. All patients participating in the study will receive a standardized intraoperative analgesic protocol according to our local institutional cardiac ERAS protocol.
11. A member of the anesthesia block team (who was not involved in the block procedure) will see the patient on postoperative day (POD) 1 to monitor for any complications of the block.
12. The remainder of data collection will occur electronically.
13. A member of the research team will call the patient 90 days after surgery to administer a Brief Pain Inventory Short Form.
14. All medications taken for analgesia at home regularly, prior to arrival on the day of surgery, and perioperatively (until 72 hours postoperatively) will be recorded.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

11.1.1 Data Collection Forms

All study data will be collected by a study team member on a standardized case report form (CRF) and stored within the university approved data collection site OnCore. Data entry into electronic format will take place on a private computer away from potential viewing by non-study personnel. The paper and electronic data will be kept in a locked office in the Department of Anesthesiology. The computer will be pass-coded and linked to a secure Anesthesia Department server to allow access only to approved study personnel. All identifiable data will be destroyed as soon as it is no longer required. De-identified

data will be retained for 7 years per UW-Madison best practices. For statistical analysis, de-identified data will be sent to biostatistician via email as a password protected encrypted zip file.

11.1.2 Data Management Software System(s)

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will be entered into the following data management software system(s) to ensure consistent data entry and data quality. Clinical data will be entered directly from the source documents.

OnCore

The Online Collaborative Research Environment (OnCore) Clinical Trial Management Software (CTMS) will be used for this study.

OnCore is a web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data (and Safety) Monitoring Committee(s) and statisticians. This software provides protocol and subject management functions (e.g., subject scheduling; screening; data organization), maintains updated forms, addresses budget development, billing and fiscal management, generates summary reports, and provides essential links with research administration and electronic medical records systems. The OnCore system eases the burden of the individual researcher and unifies protocol management within research programs and across research sites, enhancing protocol integrity and regulatory compliance efforts.

The OnCore Support Team works with the investigator, statistician, and study team to ensure the relevant, applicable study data are collected and managed in a secure web-based system with restricted access using the software electronic case report forms (eCRFs). The OnCore Support Team will work with the study team to ensure the appropriate data is exported for analysis, but will not perform the analysis.

11.2 Confidentiality and Privacy

All study staff engaged in the conduct of this project have completed training on the protection of human subjects and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key personnel (i.e., Principal Investigator, individuals involved in identifying/recruiting subjects, obtaining informed consent, or interacting and intervening with subjects) have undergone Good Clinical Practice (GCP) training.

Information about study subjects will be kept confidential and managed according to HIPAA requirements. All subjects will sign an informed consent document and a HIPAA authorization form or a combined informed consent and HIPAA authorization form> that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

Confidentiality will be protected to the extent possible by coding subject data and storing electronic data on password-protected anesthesiology department network computers and hard copy data in a locked study office until destruction. We will also utilize a secure information storage program OnCore. All hard copy data (source documents, signed consent forms, CRFs) will be stored in a locked study office. For statistical analysis, data will be de-identified on an excel spreadsheet that will be sent via email as a password protected encrypted zip file to the statistician.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: representatives of the IRB, DSMB/DSMC, and federal oversight agencies. The clinical study site will permit access to such records.

11.3 Records Retention

It is the investigator's responsibility to retain study essential documents for a minimum period of 7 years following completion of the study per UW-Madison institutional policy.

11.4 Publication and Data Sharing Policies

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

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

12.0 STUDY ANALYSIS

12.1 Statistical Hypotheses

12.1.1 Primary Efficacy Endpoint(s):

Patients who receive local anesthetic via PIFB will demonstrate lower total opioid use during the initial 72 hours postoperatively compared to patients in the sham-control group.

12.1.2 Secondary Efficacy Endpoint(s):

- Patients who receive local anesthetic via PIFB will have a decreased intraoperative opioid requirement compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will have lower maximum and mean pain scores during the first 72 hours postoperatively and at 90 days postoperatively compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate lower daily opioid use during the initial 72 hours postoperatively compared to patients in the sham-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significant reduction in time to extubation compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significantly decreased time to return of bowel function compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significantly reduced rate of postoperative delirium compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significantly decreased ICU length of stay compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significantly decreased hospital length of stay compared to patients in the saline-control group.
- Patients who receive local anesthetic via PIFB will demonstrate a significantly decreased persistent use of opioids at 90 days postoperatively compared to patients in the saline-control group.

12.2 Sample Size Justification

We conducted a retrospective chart review on prior single valve and CABG procedures utilizing a median sternotomy over a two-month period at our institution to characterize opioid consumption in our current patients. We found the average total opioid consumption in the first 72 hours following sternotomy was 245

MME (morphine milligram equivalents) +/- 87mg. We concluded that a 25% reduction in postoperative opioid requirements would be clinically significant, which is in line with what prior studies have utilized[27]. Therefore, using a type 1 error rate of 0.05, power of 90%, and a sampling ratio of 1:1 between study arms, we calculated a sample size of 86 patients (43 patients per group). To compensate for potential dropouts and incomplete data, a total of 100 patients (50 patients in each group) will be targeted for enrollment.

12.3 Subject Population(s) for Analysis

- Intention-to-Treat (ITT): all randomized subjects
- Safety Analysis Dataset: all randomized subjects who received the required study intervention.
- Protocol-compliant Population: all randomized subjects who received the required study intervention.

12.4 Statistical Methods

The primary endpoint is total postoperative opioid requirement within 72 hours. Total opioid requirement will be measured in morphine equivalents, presented as mean +/- standard deviation, and compared between study groups using a two-tailed independent samples t-test. Secondary outcomes (total intraoperative opioid requirement, mean and maximum 72-hour postoperative pain scores**,** and pain score 90 days postoperatively) will also be presented as mean +/- standard deviation and compared using independent samples t-tests. Daily postoperative opioid use and mean pain scores on POD1, POD2, and POD3 will also be compared separately with Holm-Bonferroni correction. For pain scores, we will compare mean VRS and average each patient's score within each day before averaging across days. We recognize the debate in the literature about how to analyze pain scores. In the previously referenced randomized controlled trials[19,20], the authors used mean scores so we will do so as well.

Continuous secondary outcomes that we expect will not be approximately normally distributed (duration of mechanical ventilation, time until return of bowel function, ICU length of stay, hospital length of stay) will be presented as median with interquartile range and compared using Mann-Whitney tests. Categorical variables (delirium, chronic opioid use) will be presented as counts or as percentages and will be compared using Fisher's exact test. For all planned comparisons with parametric tests, non-parametric equivalents will be substituted if the assumptions of parametric testing are found to be violated before testing.

12.5 Handling of Missing Data

Guidelines promulgated in the National Research Council report on handling of missing data will be followed[.28,29].

13.0 RISK/BENEFIT ASSESSMENT

13.1 Known Potential Benefits to the Subjects

Possible benefits of participating in this research study include improved postoperative analgesia, decreased opioid requirements and related side effects, shorter intensive care unit and hospital length of stay, and a decreased risk of developing chronic pain related to the surgery.

13.2 Known Potential Risks

PIFB risks

Possible risks of a pecto-intercostal fascial plane block include bleeding, infection, failed block, vascular injury, or pneumothorax[30]. However, compared to the transversus thoracic muscle plane block, the PIFB is more superficial and thought to be safer due to the increased distance between the fascial plane and the pleura and internal thoracic vessels[31]. No serious block related complications have been reported with the

PIFB[19,20]. Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions in this group of drugs is related to excessive plasma levels due to overdosage, unintentional intravascular injection or slow metabolic degradation. Central nervous system reactions as a result of these may include restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions, drowsiness, unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered. Cardiovascular system reactions from high doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology (including severe hypotension). Neurologic effects following procedures may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.

In clinical trials utilized for FDA approval of Exparel (liposomal bupivacaine), the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting. The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain. The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Risks associated with loss of confidentiality
There is a risk that information recorded about subjects will be shared with people who would not normally have access to this information.

Unknown risks
This study may involve risks to the subject which are currently unforeseeable. We will inform subjects as soon as possible if we discover any information that may affect the subject's health, welfare, or decision to be in this study.

13.3 Risk/Benefit Analysis

PIFB:

The risk of infection will be minimized by using the standard of care for regional anesthesia including a mask and sterile gloves for the provider, sterilizing the field of the block, and using sterile equipment. The

risk of bleeding will be minimized by adhering to the American Society of Regional Anesthesia evidenced-based guidelines for regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy[32]. Despite not being a neuraxial technique, we will use the more conservative guidelines specific for neuraxial techniques to further minimize the risk of significant bleeding. Performing the procedure under ultrasound guidance allows us to identify all important adjacent structures to avoid injury to surrounding tissues and blood vessels.

Blinding:

All of the patients enrolled in the study will receive wrist bands indicating the possible use of liposomal bupivacaine in order to avoid the use of any additional local anesthetic or regional intervention for 96 hours. To minimize the risk associated with blinding, the co-principal investigators will be available to be contacted by other caregivers for unblinding in the situation where that becomes necessary for patient safety.

Failed block:

The risk of a failed block and inadequate analgesia will be minimized by the availability of supplemental oral and intravenous analgesics.

In light of the mitigation strategies described above we believe the risk-to-benefit ratio is acceptable.

14.0 DATA AND SAFETY MONITORING

14.1 Adverse Event (AE) Definition

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject enrolled in this study, including any abnormal sign, symptom, or disease temporally associated with the PIFB or other study procedure that appears or worsens during the study or study follow-up period. AEs may be anticipated (i.e. redness or soreness at the injection site) or unanticipated (i.e. bleeding, infection, allergic reaction). Adverse event information will be collected throughout the entire study, and through resolution of the AE if present.

Study staff will monitor for AEs by following up with the patient on post-operative day (POD) 1 and POD 90, electronic chart review, and with additional follow-up as needed related to any concerns for AEs from the primary care teams. All AEs will be recorded on a study data sheet and in the electronic database by a study investigator or study staff. In the event of an unanticipated AE, the primary anesthesia or intensive care unit team caring for the subject will intervene as deemed appropriate.

14.2 Serious Adverse Event (SAE) Definition

A serious adverse event (SAE) is defined as any adverse event that meets one of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongs existing hospitalization
- Results in significant or persistent disability or incapacity
- Results in a congenital anomaly/birth defect

14.3 Classification of an Adverse Event

14.3.1 Severity of Event

The severity of all adverse events will be assessed according to the following scale:

- Mild: not requiring treatment or intervention
- Moderate: resolved with treatment/intervention
- Severe: inability to carry on normal activities and required professional medical attention

14.3.2 Relationship to Study, Study Procedure(s) and/or Study Intervention(s)

A co-principal investigator will determine the relationship of any adverse events to the research intervention using the following scale:

- Definite: AE is clearly related to the study procedures
- Probable: AE is likely related to the study procedures
- Possible: AE is possibly related to the study procedures
- Unlikely: AE is doubtfully related to the study procedures
- Unrelated: AE is clearly not related to the study procedures

14.4 Reporting AEs and SAEs

Non-serious adverse events will be recorded if they occur from the time the study procedure begins to the patient's hospital discharge. All serious adverse events will be recorded if they occur from the time that the subject provides informed consent through and including the 90-day follow-up phone call. All adverse events will be communicated to and between the co-principal investigators.

Given the minimal risk associated with the use of PIFB, no serious adverse events are anticipated. If a SAE occurs, the study co-principal investigators will be immediately notified and further enrollment in the study will be halted until a full explanation of the cause of the event and its relationship to the PIFB and/or study procedure is understood. The IRB will be notified and re-initiation of study enrollment will not occur until approved by the IRB.

14.5 Unanticipated Problems

An unanticipated problem (UP) is defined as an event that meets all of the following criteria:

- Unexpected in severity, nature, or frequency given the research procedures and the characteristics of the subject population
- Related or possibly related to participation in the research study:

The investigator will report UPs to the reviewing IRB and lead Principal Investigator (PI). The UP report will include the following information:

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

- Report UPs within the timeframe(s) specified by the IRB(s) of record.

14.6 Other Reportable Events

Reporting timeframes begin when the site learns of the occurrence of the event.

Event	Definition	Reporting

Breach of confidentiality	The exposure of any study information or communications directly related to a study subject to anyone not named as study staff or the release of a study subject's identifiable information to study staff who were not specified to receive such information in the protocol or IRB application.	Treat as major deviation (below)
Protocol deviation	A deviation is an incident involving a departure from the IRB-approved protocol in the actual conduct of the study. Deviations may result from the action of the participant, investigator, or staff.	See below
Major deviations	Deviations are considered major when the unapproved change(s) in previously approved research activities, implemented without IRB approval, may potentially adversely affect subjects' rights, safety, welfare, or willingness to continue participation, or affect the scientific design of the study and/or the integrity of the resultant data.	Treat as an Unanticipated Problem (above)
Minor deviations	Deviations are considered minor when the unapproved change(s) in previously approved research activities, implemented without IRB approval, do not adversely affect subjects or the integrity of the study data.	Sites are to report cumulative events to AE Coordinator at time of continuing review.
Protocol violation	An incident involving an intentional deviation from the IRB-approved protocol that was not implemented in response to an emergency situation and that may impact a subject's rights, safety, and/or welfare, makes a substantial alteration to risks to subjects, or affects the scientific design of the study and/or the integrity of the resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing non-compliance with the federal regulations and guidelines for ethical conduct of human subject research.	Treat as an Unanticipated Problem (above)
Protocol Exceptions	A protocol exception is an IRB-approved deviation for a single subject or a small	Protocol exceptions must be approved by local IRB prior to implementation.

	group of subjects, but is not a permanent revision to the research protocol.	

14.7 Safety Oversight

After 15 subjects have been recruited, the study data will be reviewed by an independent anesthesiologist, blinded to study arm assignment, to ensure that no safety concerns exist. In the unlikely event that there is a safety concern, study recruitment will be halted and an independent Data Safety Monitoring Committee (DSMC), consisting of a minimum of three qualified practitioners, will be convened to evaluate the safety concern and make recommendations regarding changes to the study methods or termination of the study.

Provided that no safety concerns exist after 10 patients, the independent anesthesiologist will periodically monitor the data through the end of the study.

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