PECS Block vs. Multimodal Analgesia for Prevention of Persistent Postoperative Pain in Breast Surgery

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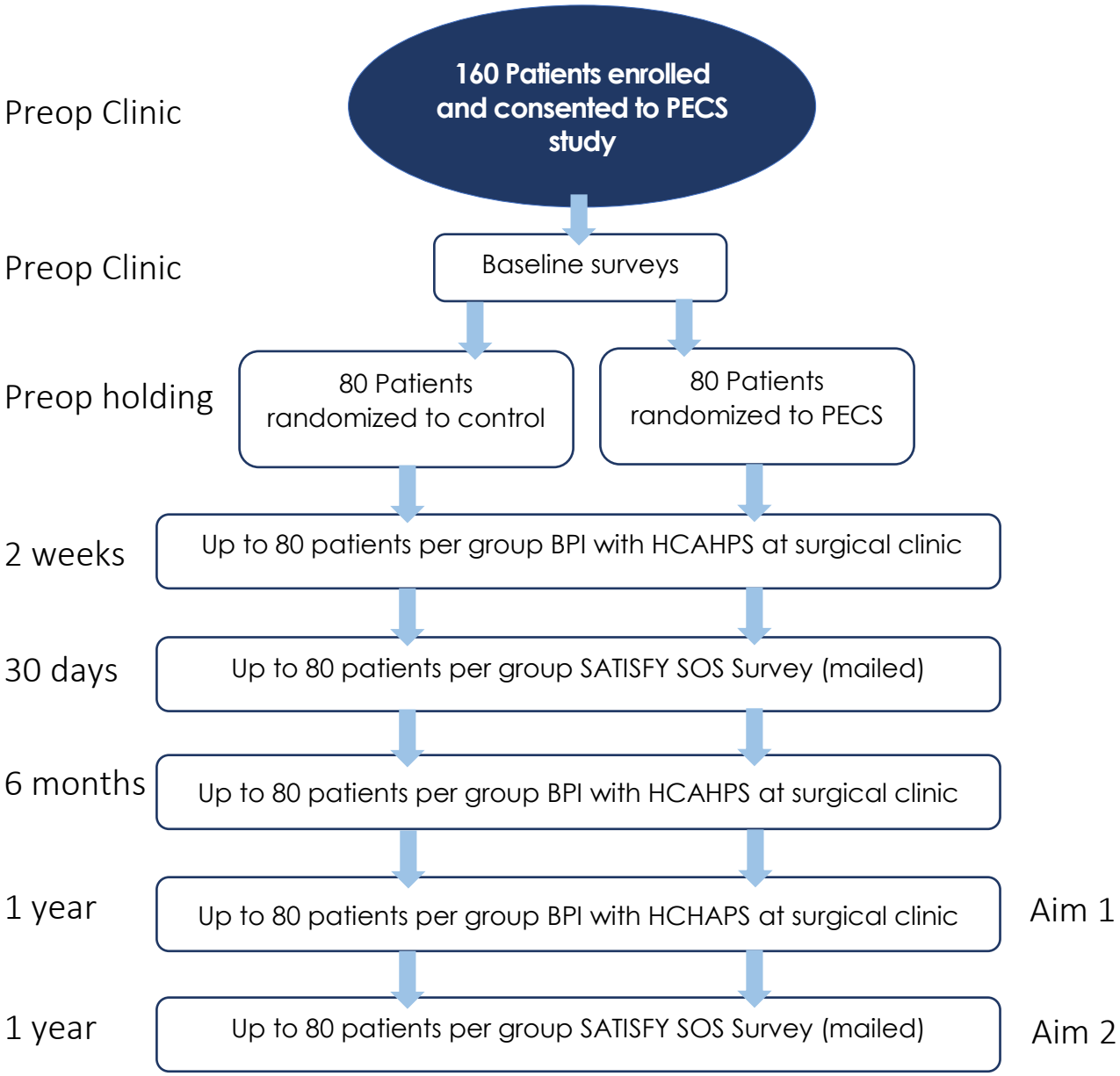
SCHEMA



Abstract

Introduction: Persistent postoperative pain affects up to 60% of patients after breast cancer surgery. Breast sparing surgical options such as lumpectomy with sentinel lymph node biopsy are still associated with persistent postoperative pain rates above 20%. This can lead to limitations in ability to function and work as well as deterioration of quality of life and higher medical care costs. Paravertebral nerve blocks have been shown to significantly decrease this risk, but paravertebral blocks are difficult to perform and can be associated with significant morbidity. In 2012 Dr. Rafael Blanco introduced the pectoral nerve block (PECS) as an alternative method of decreasing pain after breast surgery. While it has been shown to decrease acute postoperative pain, it is unknown if it decreases chronic postoperative pain in the longer term.

Methods: In this double blinded randomized placebo-controlled trial, 160 subjects scheduled for breast surgery involving the axilla will be administered a multimodal pain regimen including acetaminophen, dexamethasone, celecoxib, and gabapentin. Eighty subjects will also be randomized to receive a PECS I and II block preoperatively. All patients will receive general anesthesia including fentanyl for analgesia (or other opioid if allergic to fentanyl). Subjects will be assessed at baseline and 1 year postoperatively with a modified Brief Pain Inventory to look for differences between cohorts (with PECS block or without), for incidence and severity of persistent postoperative pain. All patients will also be assessed at baseline and 1 year using Veterans RAND 12 questionnaire collected with the SATISFY SOS survey for difference in quality of life (WUSTL IRB# 201203088, NCT02032030).

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1 BACKGROUND

Breast cancer is the second most common cancer among women in the United States with approximately 250,000 new cases each year.(1) The primary treatment is surgical intervention, which can lead to high rates of persistent postoperative pain (PPP).(2) Twenty-five to 60% of patients will experience chronic pain depending on treatment.(3) For modified radical mastectomy, 50% of patients develop chronic pain with impaired quality of life.(4) Breast conserving therapy (partial mastectomy) is associated with less pain overall, but still results in a significant PPP rate of 25%. Due to an average 5-year survival rate of 89%, there are nearly 3 million women living in the US who have current or treated breast cancer. (5) Consequently, chronic pain following breast cancer surgery likely affects over 500,000 women, leading to hundreds of millions of dollars in medical costs as well as loss of ability to work and deterioration in quality of life. (6) Paravertebral nerve blocks have been shown to substantially decrease the incidence of PPP by 44-86%. (7,8,9) However, paravertebral blocks are difficult to perform and can be associated with significant morbidity. In 2012 the Pectoral Nerve blocks I and II (PECS I and II) were introduced as safer and easier methods of decreasing pain after breast surgery.(10) While PECS blocks have been shown to decrease acute postoperative pain,(11) it is unknown if they decrease pain in the longer term.

Our long-term goal is to optimize the perioperative pain management of breast cancer surgery, to both minimize acute and chronic postoperative pain and maximize patient satisfaction in the most cost effective manner. Our hypothesis is that PECS blocks, compared with multimodal analgesia, will decrease persistent postoperative pain and improve patient reported quality of life. The rationale is that since paravertebral blocks have been shown to decrease both acute and chronic postoperative pain, and PECS blocks have been shown to decrease acute pain, it is likely that PECS blocks also decrease chronic postoperative pain.

2 OBJECTIVES

2.1 Primary Objective

To determine whether PECS I and II blocks decrease persistent postoperative pain compared with multimodal analgesia. Pain will be measured by the Brief Pain Inventory.

2.2 Secondary Objective

To determine the effects of PECS blocks on postoperative quality of life, as self-reported by patients. QOL will be measured by the Veterans RAND 12 questionnaire collected in the SATISFY-SOS study.

3 PATIENT SELECTION

3.1 Inclusion Criteria

1. Scheduled to undergo one of the following elective breast cancer surgeries at Barnes-Jewish Hospital:
   a. unilateral axillary dissection
   b. unilateral modified radical mastectomy
   c. mastectomy with same day unilateral reconstruction
   d. unilateral sentinel lymph node biopsy (SLNB)
   e. partial mastectomy with unilateral SLNB
   f. simple mastectomy with unilateral SLNB
2. At least 18 years of age.

3. Able to understand and willing to sign an IRB-approved written informed consent document.
4. Enrollment in the SATISFY-SOS study (WUSTL IRB# 201203088, NCT02032030).

3.2 Exclusion Criteria

1. Planned for bilateral axillary or bilateral reconstruction surgery.
2. Previous surgery on the surgical breast and/or axilla with the exception of partial mastectomy or sentinel lymph node biopsy.
3. Pre-existing pain in the axilla affecting ability to use extremity for activities of daily living or requiring medication for treatment
4. Current or past medical history of liver disease or cirrhosis with an elevated INR >1.4 or currently elevated transaminase levels.
5. Known contraindications to peripheral nerve block placement.
6. Pregnant or breastfeeding.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to amide local anesthetics, acetaminophen or dexamethasone.
8. Planned additional surgery to the surgical breast or axilla in the next year (exception would be minor surgery to breast but not axilla such as simple tissue expander replacement or lumpectomy)

3.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial.

3.4 Alternative to study enrollment in SATISFY-SOS

Patients that choose not to enroll in the SATISFY-SOS trial and thus ineligible to participate in this study will be given high quality standard of care with medications and regional anesthesia prescribed at the discretion of the surgeon and anesthesiologist. Currently, most patients undergoing elective, surgical breast procedures are not administered a nerve block, but it is available on request.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient research identification number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team

6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Randomization and Blinding

There will be two blocks of patients based upon type of surgical breast procedure. Block A will contain patients that are scheduled for surgical breast reconstruction, axillary dissection, and modified radical mastectomy. Block B will contain patients scheduled for all other eligible breast procedures. Each block of consented subjects will undergo separate 1:1 randomization to either PECS block or no PECS block. All subjects in both blocks will undergo identical preoperative, intraoperative and postoperative analgesic regimen, surveys and data collection. An unblinded member of the study team will generate the randomization assignment list for each block using online Research Randomizer (https://www.randomizer.org/). The randomized list for both cohorts will be provided to Investigational Drug Services (IDS), who will provide study drug syringes containing either bupivacaine or placebo per the randomization assignment. Prior to the participant's surgery, the research coordinator will provide Investigational Drug Services (IDS) with a copy of the subjects signed informed consent and study UPN number, along with appropriate Surgery Block as determined by type of planned surgical procedure. The patient, regional anesthesiologist, data collection team, anesthesia team, surgeon, and postoperative acute care unit (PACU) team will be blinded to group assignment. The regional anesthesiologist will also be provided with a sealed envelope that indicates the study drug, if it should be considered in the subject's best interest to break the blind. The blinding will be opened to the statistician following study completion for all subjects. The blind will be opened completely after follow-up is complete.

5 METHODS

This study is a pragmatic pilot double-blinded randomized placebo controlled trial that will enroll up to 160 evaluable patients who will undergo elective breast cancer surgery at Barnes Jewish Hospital North. Participants will be randomized to receive either preoperative PECS blocks or sham placebo PECS blocks. Both groups will receive multimodal analgesia in addition to the study procedure. Participants will be assessed at enrollment with baseline surveys, then later at 2 weeks, 30 days, 6 months, and 1 year after surgery. The primary outcome measure will be the severity of postoperative pain at 12 months by modified Brief Pain Inventory (BPI). Study patients will also be enrolled in the Systematic Assessment and Targeted Improvement of Services Following Yearly Surgical Outcomes Surveys (SATISFY-SOS) trial clinicaltrials.gov (HRPO# 201203088, NCT02032030). Data from the SATISFY-SOS study will be used to assess patients' quality of life at 1 year and to provide additional baseline information for confounder adjustment. Figure 1 outlines the study design of this proposed research. The trial will be registered at clinicaltrials.gov after IRB approval. Data reports from the SATISFY-SOS study will be generatedatvarious time points throughout the study for subjects enrolled to this protocol.

5.1 Primary Intervention – PECS Blocks

Preoperative performance of PECS blocks is the primary intervention to which patients will be randomized. For patients in the PECS group, a PECS I and II block will be administered with standard monitoring per usual protocol in either the preoperative holding area, or in the operating room after administration of general anesthesia before surgical incision. For unilateral surgeries, a PECS I block will be performed with 0.15mL/kg of 0.375% bupivacaine

(maximum 10mL). The PECS II block will be performed with 0.3 mL/kg of the same solution (maximum 20mL). If there is a contralateral surgery (simple mastectomy) a PECS II block will also be performed on the other side with 0.2mL/kg of 0.375% bupivacaine (maximum 20mL). It is common for patients scheduled for a modified radical mastectomy to also be scheduled for a prophylactic simple mastectomy on the other side. For patients in the multimodal group a sham block (normal saline) will be placed either in the preoperative holding area, or in the operating room, with timing based on maximizing operating room efficiency. Timing of block placement will not be randomized. The regional anesthesia team will be responsible for all block and sham block placement. To ensure blind integrity, study drug syringes will be marked only "study drug" and subject number. If the anesthesia team suspects local anesthetic toxicity, the regional anesthesia team will break the blind and be asked to assist with evaluation and treatment.

5.2 Multimodal Analgesia and Perioperative Protocol

In order to minimize treatment variability, the perioperative analgesic regimen will be encouraged, but not mandated for research subjects at the discretion of the anesthesia and surgical teams. Gabapentin 300mg, celecoxib 200mg, and acetaminophen 1000mg will be administered to all patients following arrival to the preoperative holding area. If the patient is allergic to celecoxib or sulfa, naproxen 500mg PO will be substituted. If the patient is intolerant to NSAIDs or has a GFR <60 (not including GI upset for celecoxib), celecoxib/naproxen will be held. If the patient is >65 years old but has a GFR >60 celecoxib/naproxen will not be held, but a reduced dose of celecoxib 100mg or naproxen 250mg will be administered. If the patient is over 65 years old or has a GFR <60 gabapentin will be held. Subjects already taking acetaminophen, gabapentin or celecoxib on a routine basis prior to study participation may take the pre-study home medication dosage, or the per protocol dosage, whichever is higher. If a patient is intolerant to the higher protocol dosage, the lower home dosage will be used. Other home medications will not be altered as a result of study participation. Standard of care block and pre anesthetic sedation will be at the discretion of the regional and general anesthesiology teams.

Standard of care general anesthesia will be administered to all patients at the discretion of the attending anesthesiologist and nurse anesthetist. This is performed for all patients regardless of enrollment in the study. Intraoperative opioid medication will be limited to fentanyl unless the patient is intolerant to fentanyl. In that case, it will be at the discretion of the anesthesiologist. Fentanyl is the standard of care intraoperative pain medication for all surgeries at BJH and is administered to over 95% of patients. All patients will receive the same postoperative order set for the PACU and hospital floor. The PACU postop order set consists of fentanyl followed by oxycodone as needed for patients with anticipated same day discharge to home. If the patient is scheduled for hospital admission following surgery, hydromorphone may also be administered following fentanyl administration. This is the most commonly used opioid pain medication regimen at BJH. Patients will receive a standard antiemetic regimen including scopolamine patch preoperatively (if age < 65 and no history of glaucoma), 4mg IV ondansetron intraoperatively, 8 mg dexamethasone IV after induction of general anesthesia as needed, and postoperative orders for an additional dose of ondansetron as needed. Further antiemetics will be given at the discretion of the anesthesiologist.

Following surgery, patients will receive oral acetaminophen 1000mg Q6 hours and celecoxib 200mg BID for the first 3 days as needed. Gabapentin 300mg will be administered at bedtime while hospitalized if the patient is not discharged on the same day as surgery. Home oxycodone will be prescribed per the discretion of the surgical attending who will also be blinded to group assignment. If the patient is intolerant to oxycodone, hydrocodone/acetaminophen may be substituted and scheduled acetaminophen will be held. After the first three days, adjuvant doses will be decreased to acetaminophen 1000mg Q8 hours and celecoxib 100mg BID as needed. This dosage will continue until the first postoperative visit (2 weeks postoperatively) as long as the patient is experiencing pain. Gabapentin will not be prescribed for any patient with preexisting kidney disease (GFR < 60) or with age > 65 years. Celecoxib will be administered at a reduced dose (100mg) for any patient with age > 65 and a normal GFR (>60) as long as the patient is experiencing pain. Naproxen 500mg or 250mg (age >65) BID will be substituted for celecoxib in patients with sulfa allergies. Naproxen will be held for any patient with history of NSAID

intolerance. Postoperative prescriptions may be modified to account for comorbidities instead of excluding patients from the study in order to reflect real world practice. Patients who are not able to take gabapentin, acetaminophen, dexamethasone, ondansetron, celecoxib, or scopolamine will not be prescribed these medications, but may still participate in the study. Medications and dosages may be modified by the surgeon or blinded acute pain service as necessary to treat the patient's pain if the patient is intolerant to any study medications, has preexisting chronic pain, or if the surgeon or blinded acute pain service determines that modified medications and dosages is the best treatment for the patients' pain.

5.3 Evaluability

Follow up data collected for subjects that undergo additional breast surgery (exception would be minor surgery to breast but not axilla such as simple tissue expander replacement or lumpectomy) before 6 month and 1-year follow-ups, will not be considered as evaluable and will be excluded from analysis. These subjects will be considered as withdrawals prior to study completion at 12 months. Only data collected prior to the additional breast surgery is considered evaluable. Additional patients will be recruited in order to accrue the targeted number of complete and evaluable study subjects before the enrollment period ends. A complete dataset requires collection of surveys through-out the study period of approximately 1 year.

5.4 Duration of Follow-Up

Patients will be followed for one year after surgery or until an additional major breast surgery is performed, whichever occurs first.

5.5 Risks

The risks associated with this study are low. PECS blocks have been performed on many patients in previous studies with no major complications. The blocks have also been performed on over one hundred patients for breast and other procedures at BJH with no major complications. The regional anesthesia service at Barnes Jewish Hospital performs over 3000 peripheral nerve blocks a year with no known recent major complications. Since the target structures are fascial planes and not discrete nerves the possibility of nerve damage from the blocks is very low. Local anesthetic toxicity risk is also likely very low from PECS blocks due to stringent weight based dosing and ultrasound monitoring of block placement. Hematoma is possible any time a needle is used to inject a patient, but as the breast is a compressible site a hematoma would be readily apparent and easily treated. We follow very conservative ASRA guidelines for anticoagulants with regard to placement of nerve blocks which further decreases the chance of hematoma. Unlike other regional anesthetics such as epidural block, a hematoma at the PECS block site would be unlikely to cause any lasting harm. Infection is another risk frequently cited for regional anesthesia. The procedure will be performed by board-certified, trained anesthesiologist with extensive experience in using strict sterile technique. To date, there have been no reports of infection from a single shot peripheral nerve block performed at Barnes-Jewish Hospital by the regional anesthesia team. As part of the informed consent process for this study, patients will be informed of the rare risks of hematoma, infection, or drug reaction. In the unlikely event that serious side effects occur, they will be documented and will be reported to the human research protection office and to the study's data safety monitoring board. Participants will not be financially compensated for their participation. The patients' insurance will be billed for PECS blocks if performed as they are a standard procedure for prevention and treatment of acute pain. Those that choose not to participate will receive standard treatment per surgeon discretion. There is also a rare risk of breach of confidentiality.

6 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 6.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

6.1.9 Anticipated Adverse Events

These are anticipated, study-related AE/SAEs and will be tracked and reported annually. Refer to section 6.1.5 for unanticipated AE/SAE.

PECS Block:
Likely / Common
Mild
- Slight bleeding at the injection site

Less Likely / Less Common
Mild
- Small pool of blood forming around the injection site
- Bruising

Rare
Life Threatening
- Toxic reaction to the numbing agent causing heart attack

Serious
- Nerve damage
- Infection at the injection site

Ondansetron:
Likely / Common
Mild
- Constipation
- Headache
- Dry mouth

- Tiredness

Less Likely / Less Common

Mild

- Diarrhea
- Elevated liver function tests, which means the liver may not be functioning properly and can cause fatigue and jaundice (yellowing of the skin and eyes)

Rare

Serious

- Serious irregular heartbeats
- Low potassium in the blood, which can increase the risk of irregular heartbeats
- Fever
- Severe allergic reaction, such as rash, hives, fever, difficulty breathing, and low blood pressure
- Seizures
- Temporary blindness

Gabapentin:

Likely / Common

Mild

- Dizziness
- Drowsiness
- Fatigue

Less Likely / Less Common

Serious

- Ataxia

Rare

Life Threatening

- Rhabdomyolysis, which is a rapid breakdown of muscle tissue causing weakness, pain, and vomiting.
- Suicidal thoughts or behavior
- Drug reaction that can cause whole body inflammation which may damage organs.

Celocoxib:

Likely / Common

Mild

- Headache

Less Likely / Less Common

Mild

- Fever
- Upset stomach
- Joint pain
- Cough
- Vomiting
- Diarrhea
- Gastroesophageal reflux which causes indigestion and a burning sensation in your chest and throat
- Sinusitis, an infection of the spaces in the bones of your cheeks and forehead that cause pain and sometimes mucus drainage at the back of your throat.
- Abdominal pain

Rare

Serious

- Elevated liver function tests, which means the liver may not be functioning properly and can cause fatigue and jaundice (yellowing of the skin and eyes)
- Anemia
- Serious rashes: called erythema multiforme or exfoliative dermatitis. Both are severe rashes that can occur as an allergic response to a medication.

Life Threatening

- Stevens-Johnson syndrome is a severe skin condition in which the layers of your skin separate because cells between them die as a reaction to a drug.

Acetaminophen:

Likely / Common

- None

Less Likely / Less Common

Mild

- Rash
- Disorientation
- Dizziness

Rare

Life threatening

- Liver Disease
- Stevens-Johnson syndrome is a severe skin condition in which the layers of your skin separate because cells between them die as a reaction to a drug.
- Toxic epidermal necrolysis is a severe skin condition in which the layers of your skin separate because cells between them die as a reaction to a drug.
- Throat swelling
- Agranulocytosis – Failure to produce white blood cells, which means your body would not be able to fight off an infection.
- Thrombocytopenia – Decreased clotting cells
- Kidney Disease
- Pneumonia

Hydromorphone/fentanyl/oxycodone/hydrocodone:

Likely / Common

Mild

- Urinary retention
- Sedation
- Nausea
- Constipation
- Dry mouth
- Dizziness
- Agitation
- Euphoria

Less Likely / Less Common

Serious

- Rapid heart rate
- Dysphoria, a feeling of uneasiness or agitation.
- Syncope, fainting due to a sudden drop in blood pressure.
- Slow heart rate
- Slowing of your breathing rate

- Depression
- Visual disturbances
- Weakness

Rare

Life threatening

- Coma
- Seizures
- Cardiac arrest or arrhythmia
- Shock

Scopolamine:

Likely / Common

Mild

- Dry mouth
- Drowsiness
- Dilation of pupil if drug contacts eye
- Dizziness
- Blurred vision

Less Likely / Less Common

Serious

- Disorientation
- Confusion

Rare

Serious

- Glaucoma, which is increased pressure inside your eyeball

Dexamethasone single dosage:

Likely / Common

Mild

- Temporary increased blood sugar
- Euphoria

Less Likely / Less Common

Mild

- Perianal itching
- Insomnia
- Sweating
- Rash

Rare

Serious

- Muscle pain
- Dysfunction of the adrenal gland, which fights infections
- Glaucoma, which is increased pressure inside your eyeball
- Hepatomegaly, an increase in the size of your liver
- Hypokalemic alkalosis: A serious change in blood chemistry
- Increased pressure in your head causing severe headache
- Increased transaminases: Liver dysfunction of unknown significance
- Psychosis, an impaired mental state where an individual has lost contact with reality.
- Fluid in your lungs
- Seizure

Naproxen:

Likely / Common

- None

Less Likely / Less Common

Mild

- Abdominal pain
- Constipation
- Dizziness
- Drowsiness
- Headache
- Heartburn
- Nausea
- Swelling

Rare

Serious

- Bleeding that occurs in your stomach and/or intestines
- Inflammation of small pockets in your bowels.
- Difficulty breathing
- Hearing disturbances
- Elevated liver function tests, which means the liver may not be functioning properly and can cause fatigue and jaundice (yellowing of the skin and eyes)

6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Timeframe for Reporting Required Events

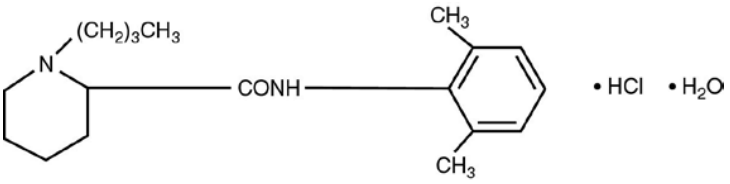
Adverse events will be tracked for 2 weeks after nerve block administration or patient discharge, whichever is later. Most patients will be discharged within 24 hours. For the purposes of this protocol, adverse events thought to be at least possibly related to surgery will not be collected and documented on CRFs.

7 PHARMACEUTICAL INFORMATION

7.1 Bupivacaine HCl

7.1.1 Bupivacaine HCl Description

Bupivacaine hydrochloride is 2-piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95% ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures.

7.1.2 Clinical Pharmacology

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.

7.1.3 Pharmacokinetics and Drug Metabolism

The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution.

The onset of action with bupivacaine HCl is rapid and anesthesia is long lasting. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

PK studies on the plasma profile of bupivacaine HCl after direct IV injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of bupivacaine HCl for caudal, epidural, or peripheral nerve block in main, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

7.1.4 **Supplier:** Bupivacaine HCl is commercially available**.**

7.1.5 Storage and Stability: Store at 20 to 25°C (68 to 77°F).

7.1.6 Administration: As described in Section 5.1**.**

7.1.7 Special Handling Instructions: None**.**

8 DATA COLLECTION

Baseline data will be collected during the CPAP visit, including demographics, age, radiation and chemotherapy history, a modified Brief Pain Inventory (Appendix A), Pain Scale (Appendix C), pain medication history, history of other sources of pain, and medical history (anxiety, depression, fibromyalgia). The modified brief pain inventory will be administered following surgery at approximately 2 weeks, 6 months, and 12 months postoperatively in coordination with routine follow up visits to the surgeon's clinic. In the event that a survey is missed a backup survey will be administered by email followed by mail and phone. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) pain domain questions will be added to the modified BPI and analyzed separately (Appendix B). The staff administering the survey will be blinded to the patient's group. As part of the SATISFY SOS study, which tracks long term postoperative outcomes, patients complete a 30-day and 1-year postoperative survey that includes the Veterans Rand 12 Item Health Survey (VR12) and the Barthel index, validated measures of quality of life and ability to perform activities of daily living. Additional data collection will include surgical procedure, medications, treatments, vital signs and any adverse events or serious adverse events that may occur in the preoperative holding area, operating room, postoperative care unit, and medical floor throughout the initial hospital stay after the surgery. Some of this data may be utilized for substudy analyses. Electronic medical record data will be extracted after completion of the primary intervention and subject's discharge from the hospital.

9 STUDY CALENDAR

	Screening	**Baseline**	**Day of Surgery**	**72 hours Post-Op**	**2 Weeks Post-Op**	**30 Days Post-Op**	**6 Months Post-Op**	**1 Year Post-Op**
Informed consent	X							
Medical history	X							
Concomitant Pain Medications	X	X	X	X	X		X	X
Randomization			X					
PECS block / placebo			X					
Multimodal analgesia			As per routine care					
Modified BPI w/HCAHPS		X			X		X	X
Pain Scale		X						
VR12		S-SOS				S-SOS		S-SOS
Barthel Index		S-SOS				S-SOS		S-SOS
AE assessment			X	X	X			

10 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	**Submission Schedule**
Original Consent Form	Prior to registration
Demographics Cancer Treatment History Pain Medication History Medical History	Prior to starting treatment
Randomization Surgery	Day of surgery
Modified BPI w/HCAHPS	Baseline 2 weeks post-op 6 months post-op 1 year post-op
Pain Scale	Baseline
VR12 Barthel Index	Baseline (S-SOS) 30 days post-op (S-SOS) 1 year post-op (S-SOS)
Concomitant Medications (Pain)	Baseline as reported by patient Inpatient 2 weeks post-op as reported by patient 6 months post-op as reported by patient 1 year post-op as reported by patient
Adverse Events	Throughout hospitalization and up to 2 weeks post-op

11 OUTCOME MEASURES

11.1 Severity of postoperative pain

Pain is inherently subjective and only quantifiable by the person experiencing the pain. By focusing patients' perception of their pain and its effects on their life with a validated survey, this design most closely mirrors how outcomes are assessed by CMS and what is most important to patients themselves. The Brief Pain Inventory (BPI) is a validated assessment routinely used for measuring chronic pain and recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement. (12) The BPI is split into two domains that assess the pain directly, and its interference with the patient's life. This allows a more complete characterization of the pain than a simple VAS score. Since the BPI is designed to assess pain in the past 24 hours, but most persistent postoperative pain studies in breast cancer consider pain over the past 7 days significant, we have modified the BPI for a 7 day benchmark. (Appendix A and B) We have also modified the language to focus on surgical site pain, neglecting pain from other areas of the body. (Appendix B) The one year BPI severity score will be the primary outcome because it is likely that the one year endpoint will be least confounded by chemotherapy or radiation administration.

At the same time as the BPI is administered additional questions from the HCAHPS survey will be asked. These questions are used by the federal government to compare hospital quality, and are published online as part of Hospital Compare on medicare.gov. The HCAHPS scores are also used to adjust payment to hospitals. The two questions directly related to pain on the survey will be asked in order to assess if PECS blocks are associated with improvement in outcomes that CMS is directly measuring.

11.2 Quality of life

Gross level of pain or pain scores are not necessarily the only relevant measure of pain for surgical patients. It is more important to both the patient and payers if pain affects the patient's quality of life. Quality of life will be assessed based on the Veterans' Rand 12 questionnaire collected as part of the SATISFY-SOS study.

12 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 6.0).

13 STATISTICAL CONSIDERATIONS

13.1 Statistical Analysis and Power

BPI scores will be compared between groups by Mann Whitney U and adjusted for known confounders and baseline pain by rank ANCOVA regression. HCAHPS pain domain scores will be analyzed similarly. Change in the 1 year VR12 score from baseline results will be compared between study groups by Mann Whitney U and adjusted for known confounders using ANCOVA regression analysis. For the purpose of powering the study a decrease in Modified BPI score (average severity domain, 0-10) of 50% (3 → 1.5) will be considered clinically significant. A sample size of 64 patients per group will have 80 percent power to detect this difference with an alpha level of 0.05 assuming a standard deviation of 3 points and using two tailed Student's T test. Our target sample size is increased to 80 patients per group to account for dropout and possible confounders including surgery type, age, radiation history, chronic pain history, and ASA score. By using rank ANCOVA regression analysis (Quade's test) we hope to decrease the within group error variance and minimize the impact of these confounders. Our goal of a 50% reduction in score is realistic for a pilot study given that previous studies with paravertebral nerve block are associated with reductions in PPP of up to 86%. (8)

13.2 Limitations

We recognize these analyses rely on subjective patient reporting of pain scores and pain's effects on quality of life. We do not intend to verify this with objective examinations of pain and decreased range of motion of the affected extremity because it is the subjective outcomes that are of importance to patients. Our sample size is powered to look for a 50% reduction of PPP by BPI average severity domain score. While this is relatively aggressive, our projected sample size of 80 patients per group is double previous studies examining paravertebral nerve block's benefits on persistent postoperative pain. (13, 8,9) Since we are powered for an outcome larger than would be clinically relevant (50% vs 20% decrease in PPP) this could be considered a pilot study if we achieve a clinically significant but not statistically significant outcome.

14 References

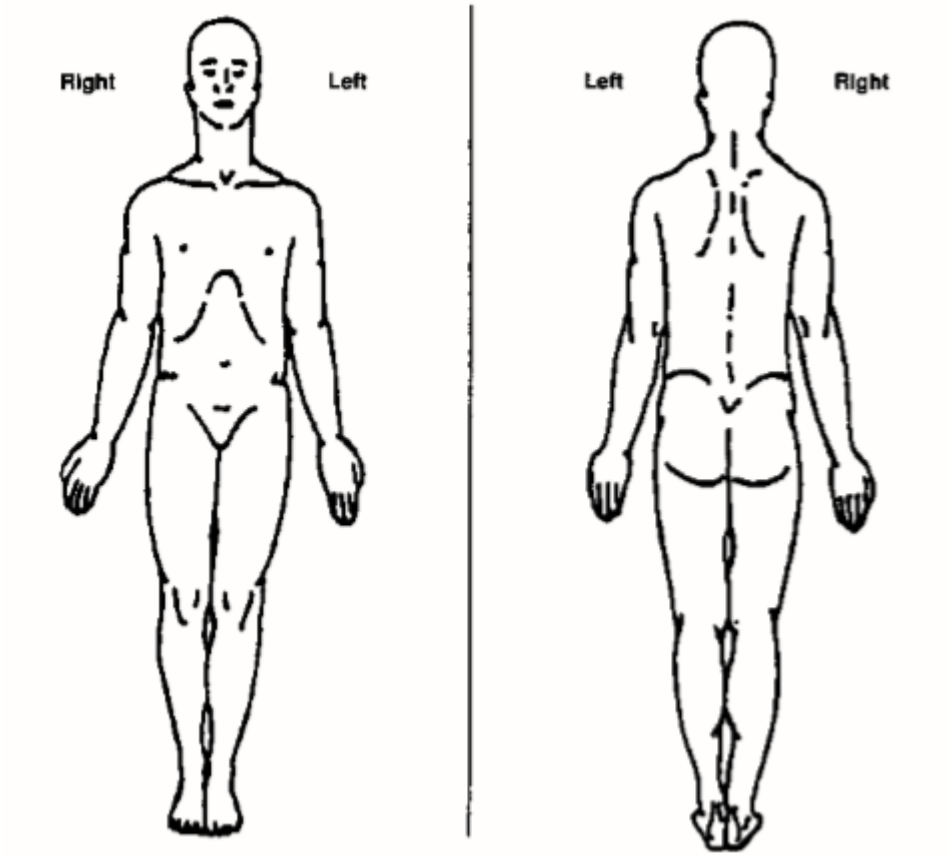
1) American Cancer Society: Cancer Facts and Figures 2016. Atlanta, Ga: American Cancer Society, 2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf Last accessed February 1, 2016.
2) Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. Jul-Aug 2012;62(4):220-41.
3) Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain2011;12:725-46.
4) Gärtner R, Jensen M-B, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA. 2009; 302: 1985–1992. Serial Solutions Bibliographic
5) National Cancer Institute SEER Stat Fact Sheets: Female Breast Cancer http://seer.cancer.gov/statfacts/html/breast.html Last accesed February 17, 2016
6) Darrell J. Gaskin, Patrick Richard. The Economic Costs of Pain in the United States. The Journal of Pain, 2012; 13 (8): 715
7) Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth. 2013;111:711–20.
8) Kairaluoma PM, Bachmann MS, Rosenberg PH, Pere PJ. Preincisional paravertebral block reduces prevalence of chronic pain after breast surgery. *Anesth Analg.* 2006;103:703–8.
9) Ibarra MM, S-Carralero GC, Vicente GU, Cuartero del Pozo A, Lopez Rincon R, Fajardo del Castillo MJ. Chronic postoperative pain after general anesthesia with or without a single-dose preincisional paravertebral nerve block in radical breast cancer surgery (in Spanish). Rev Espanola Anestesiol Reanimacion. 2011;58:290–4.
10) Rev Esp Anestesiol Reanim. 2012 Nov;59(9):470-5. doi: 10.1016/j.redar.2012.07.003. Epub 2012 Aug 29.Ultrasound description of Pecs II (modified Pecs I): a novel approach to breast surgery.Blanco R1, Fajardo M, Parras Maldonado T.
11) Reg Anesth Pain Med. 2015 Jan-Feb;40(1):68-74. doi: 10.1097/AAP.0000000000000163. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Bashandy GM1, Abbas DN.
12) Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain. 2010;149:177–93.
13) Ilfeld BM[1], Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, Mascha EJ, Xu Z, Wen CH, Morgan AC, Wallace AM. Persistent postmastectomy pain and pain-related physical and emotional functioningwith and without a continuous paravertebral nerve block: a prospective 1-year follow-upassessment of a randomized, triple-masked, placebo-controlled study. Ann Surg Oncol. 2015;22(6):2017-25.

Appendix A: Modified BPI Baseline

1**.** Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the past week

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain — Pain as bad as you can imagine

6.What treatments or medications are you receiving for your pain (including over the counter and prescription medications)?

_____

7. Are you using any narcotic prescription medications such as Hydrocodone, Morphine, or Oxycodone?

☐ Yes ☐ No

8. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No relief — Complete relief

9. Circle the one number that describes how much, during the past week pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

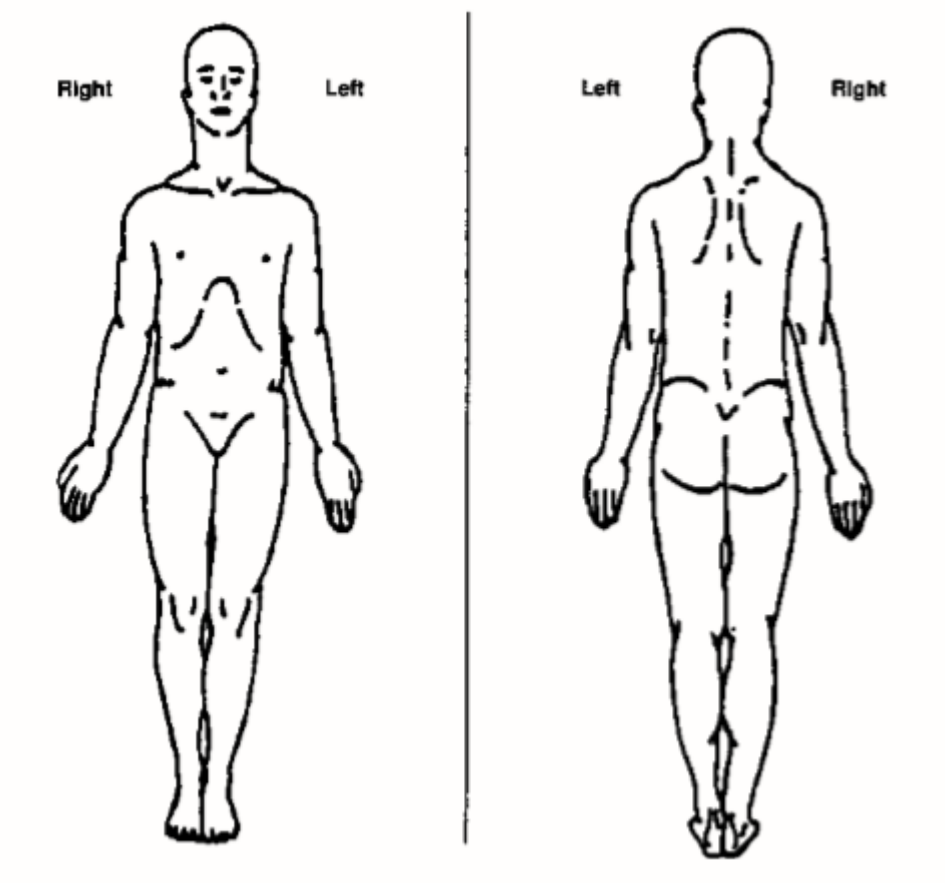
Does not Interfere — Completely interferes

Modified BPI with HCAHPS follow-up survey **PECS study – Guffey PI**

1**.** Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



2. Is your pain worst in the:

☐ Breast ☐ Armpit ☐ Neither

3. Please rate your pain from your breast or armpit surgery by circling the one number that best describes your pain at its worst in the last week.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No Pain

Pain as bad as you can imagine

4. Please rate your pain from your breast or armpit surgery by circling the one number that best describes your pain at its least in the last week.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain Pain as bad as you can imagine

5. Please rate your pain from your breast or armpit surgery by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain Pain as bad as you can imagine

6. Please rate your pain from your breast or armpit surgery by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No Pain Pain as bad as you can imagine

7.What treatments or medications are you receiving for your pain?

_____

8. Are you using any narcotic prescription medications such as Hydrocodone, Morphine, or Oxycodone?

☐ Yes ☐ No

9. In the last week, how much relief to your breast or armpit pain have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No relief Complete relief

10. Circle the one number that describes how much, during the past week, breast or armpit pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Does not Interfere — Completely interferes

11. During your hospital stay for your breast cancer surgery, how often was your pain well controlled?

1 ☐ Never

2 ☐ Sometimes

3 ☐ Usually

4 ☐ Always

12. During your hospital stay for your breast cancer surgery, how often did the hospital staff do everything they could to help you with your pain?

1 ☐ Never

2 ☐ Sometimes

3 ☐ Usually

4 ☐ Always

13. Have you had chemotherapy in the last 6 months?

☐ Yes ☐ No

14. Have you had radiation in the last 6 months?

☐ Yes ☐ No

15. Have you had surgery since your recent breast cancer surgery?

☐ Yes ☐ No

15b. If yes, where on your body was your surgery? _____

16. Are you planning on having surgery in the next year?

☐ In the next 6 months ☐ Between 6 months and 1 year ☐ Unknown time

Appendix C: Pain Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please circle the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain…	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4