Pre-operative Paravertebral Blocks to Decrease Post-operative Pain Following Mastectomy with Immediate Tissue Expander Reconstruction

JHM IRB 00075957
NCT02161705

Principal Investigator Gedge D. Rosson, M.D.
Associate Professor, Plastic Surgery and Oncology
Department of Plastic and Reconstructive Surgery
The Johns Hopkins Hospital Outpatient Center
601 N. Caroline Street, McElderry 8161
Baltimore, MD 21287
Phone: 410-955-9477
Fax: 410-614-1296
Email: gedge@jhmi.edu

Co-Investigators Jason C. Brookman, M.D.
Carisa Cooney, MPH, CCRP
Laura Gavin, M.S.
Marcelo Lacayo-Baez, M.D.
Pablo Baltodano, M.D.
Michele Manahan, M.D.
Justin Sacks, M.D.

Research Manager Carisa M. Cooney, M.P.H., C.C.R.P.

Study Coordinators Charalampos Siotos, M.D.

Study Pharmacist Andrea Weiss, R.Ph.

Research Nurse Laura Gavin, M.S., C.R.N.P.

Note: This is a modified version of the IRB-approved Bupivacaine Pain Pump Study
JHM IRB# NA_00010363

Use of Pre-operative Paravertebral Blocks to Decrease Post-operative Pain Following Mastectomy with Immediate Tissue expander Reconstruction

Original Protocol: June 25, 2013

Current Protocol: September 11, 2013

Table of Contents

1. PROTOCOL SUMMARY 6

2. SCHEMA 8

3. RATIONALE 9

4. OBJECTIVES 11

4.1 Primary Objective 11
4.2 Secondary Objectives 11
4.3 Tertiary Objectives 11

5. INVESTIGATIONAL PLAN 11

5.1 Summary of Study Design 11
5.2 Patient Population & Inclusion/Exclusion Criteria 12
5.3 Inclusion of Women and Minorities 13
5.4 Determination of Eligibility 13
5.5 Randomization 13
5.6 Blinding 13
5.7 Treatment Administration 14
5.8 Jusitification For Placebo 14
5.9 Dose Modifications 14
5.10 Supportive Care Guidelines 14
5.11 Duration of Study Participation 14

6. STUDY CALENDAR 15

7. PHARMACEUTICAL INFORMATION 16

7.1 Ropivacaine (Naropin®) 16
7.2 Placebo 22
7.3 Opioid use 23

8. ADMINISTRATIVE PROCEDURES 24

8.1 Protocol Amendments 24
8.2 Informed Consent 24
8.3 Ethics and Good Clinical Practice 24

9. ADVERSE EVENTS 24

9.1 General 24
9.2 Definitions 25
9.3 Relationship 25
9.4 Reporting Procedures 26
9.5 Data and Safety Monitoring 27
9.6 Data Management 27
9.7 Safety Meetings 27
9.8 Monitoring 27

10. STATISTICAL CONSIDERATIONS 28

10.1 Objectives 27
10.2 Study Design 29
10.3 Sample Size and Accrual 29

REFERENCES 29

APPENDICES.....31

APPENDIX A: PATIENT PAIN ASSESSMENT QUESTIONNAIRE.....32
APPENDIX B: SUBJECTIVE PAIN SURVEY.....37
APPENDIX C: BREAST-Q© RECONSTRUCTION MODULE – PREOPERATIVE QUESTIONNAIRE.....38
APPENDIX D: BREAST-Q© RECONSTRUCTION MODULE –POSTOPERATIVE QUESTIONNAIRE.....41
APPENDIX E: RAND-36 ITEM SHORT FORM SURVEY.....50
APPENDIX F: QUICK DASH QUESTIONNAIRE.....54

List of Abbreviations

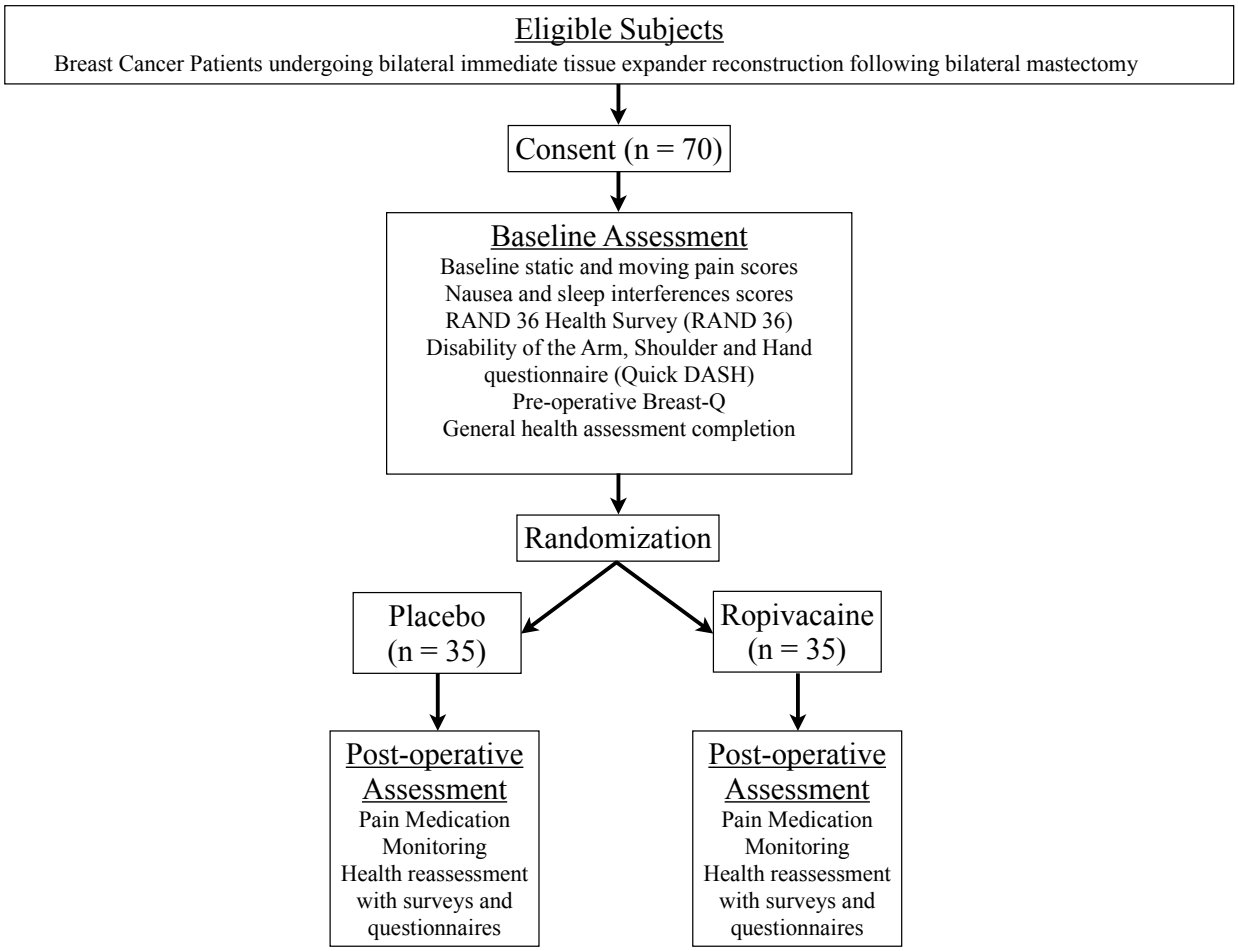
ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
cc	Cubic Centimeter
CNS	Central Nervous System
CRF	Case Report Form
DASH	Disability of the Arm, Shoulder, and Hand
DATA	Device and Technique Assessment
DIEP	Deep Inferior Epigastric Perforator
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
IV	Intravenous
mg	Milligram
mL	Milliliter
PCA	Patient-Controlled Analgesia
PO	By Mouth (Latin: *Per os*)
POE	Provider Order Entry (System)
PSEF	Plastic Surgery Education Foundation
PSI	Pounds per Square Inch
RAND	Research and Development
SAE	Serious Adverse Event
SEER	Surveillance, Epidemiology, and End Results
TRAM	Transverse Rectus Abdominus Myocutaneous

1. Protocol Summary

Full Title	Use of Pre-operative Paravertebral Blocks to Decrease Post-operative Pain Following Mastectomy with Immediate Tissue Expander Reconstruction
Short Title	Paravertebral Blocks to Decrease Breast Reconstruction Pain
Study Type	Prospective, Randomized, Double-Blind Clinical Trial
Conducted By	The Department of Plastic and Reconstructive Surgery Johns Hopkins University School of Medicine
Principal Investigator	Gedge D. Rosson, M.D.
Sample Size	Enrolled: 70 (Randomization Treatment: Placebo = 35:35)
Study Population	• Women aged 18-75 years. • Choose bilateral mastectomy followed by immediate tissue expander breast reconstruction. • Have no inflammatory breast cancers. • Be aware of the nature of her malignancy. • Understand the study purpose, requirements, and risks. • Be able and willing to give informed consent.
Accrual Period	Two Years
Study Design	Double-blind, randomized, controlled clinical trial comparing patient-reported pain and pain medication/opioid use between patients randomized to ropivacaine (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections. Candidates will have elected to undergo bilateral post-mastectomy immediate tissue expander breast reconstruction. Participants meeting inclusion criteria will be enrolled and baseline data collection completed prior to randomization and surgery. Patients will be randomized 1:1 to ropivacaine- (treatment) paravertebral blocks or subcutaneous saline-(placebo) paravertebral injections in a double-blinded design. Patient-specific surgical details will be recorded intraoperatively. Following the surgery, post-operative pain, pain medication/opioid use, and the occurrence of adverse events (AEs)/serious adverse events (SAEs) will be assessed on Days 1, 2, and 3. A clinic visit occurs on Day 7 when additional data are collected (updated medical history, pain medication/opioid use, AEs/SAEs, and study questionnaires). Long-term quality-of-life/health outcomes assessments will be done on post-operative Day 90 (±14 days), Year 2 (±14 days), and Year 4 (±14 days). The Year 2 and Year 4 follow-ups are included as tertiary endpoints to capture differences in chronic pain, and patients will be asked to complete the same questionnaires as at the Day 90 follow up.
Study Duration	Four years from initial qualifying surgery.

Study Agent/Intervention Description	Ropivacaine (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.
Primary Objective	To determine if post-operative static pain scores differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine-(treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.
Secondary Objectives	To determine if post-operative moving pain scores, opioid use, nausea, sleep interference and length of hospital stay differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine-(treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.
Tertiary Objectives	To determine if long-term changes in Quality of Life scores [the RAND-36 Health Survey, Disability of the Arm, Shoulder, and Hand (Quick DASH) questionnaire, and Breast-Q scores] differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine-(treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

2. Schema


Eligible Subjects
Breast Cancer Patients undergoing bilateral immediate tissue expander reconstruction following bilateral mastectomy
Consent (n = 70)
Baseline Assessment
Baseline static and moving pain scores
Nausea and sleep interferences scores
RAND 36 Health Survey (RAND 36)
Disability of the Arm, Shoulder and Hand questionnaire (Quick DASH)
Pre-operative Breast-Q
General health assessment completion
Randomization
Placebo (n = 35)
Ropivacaine (n = 35)
Post-operative Assessment
Pain Medication Monitoring
Health reassessment with surveys and questionnaires
Post-operative Assessment
Pain Medication Monitoring
Health reassessment with surveys and questionnaires

3. Rationale

Immediate breast reconstruction following mastectomy, when compared with delayed reconstruction or no reconstruction, has been shown to have superior results for both aesthetics and psychometric outcomes[1,2], and is less expensive than delayed breast reconstruction.[3] Additionally, the type of breast reconstruction (implant versus autologous) can affect psychosocial outcomes.[4] However, the percentage of patients who undergo immediate reconstruction following mastectomy for breast cancer remains low. The national average from the SEER database in 1998 was 15%[5], while an evaluation of the Maryland Hospital Discharge Database for 1995 through 2005 found that 28% of women in the state of Maryland had immediate breast reconstruction following mastectomy.[6] These low rates may be because patients who have mastectomy and immediate placement of tissue expanders for reconstruction have much more pain than patients who have mastectomy alone.[7]

Finding appropriate and safe ways to control post-operative pain is important. While adding non-steroidal anti-inflammatory drugs can decrease pain, it seems to increase complications. A randomized trial has shown that diclofenac significantly decreases pain and opioid use following mastectomy and immediate breast reconstruction, but significantly increases bleeding.[8]

One randomized, placebo-controlled, blinded trial found significant reductions in pain scores and analgesic consumption as well as earlier return to normal activity and better surgeon and patient satisfaction when preoperative paravertebral blockade with bupivacaine was given along with general anesthesia for varicocelectomy surgery.[9] A randomized, blinded trial in the setting of Video Assisted Thoracic Surgery, showed significant reductions on postoperative pain scores, decreased cumulative morphine consumption, increased patient satisfaction with analgesia and quicker first mobilization and time to hospital discharge.[10] Similarly, two prospective, randomized placebo-controlled trials (in the settings of hepatectomy[11] and retropubic prostatectomy[12]) also showed similar results. Further, at least six prospective randomized trials across several surgical procedures and specialties.[13, 14, 15, 16, 17, 18] have also shown a significant improvement in postoperative pain with the application of concomitant paravertebral block for analgesia. Some of these trials report on decreased consumption of postoperative analgesics[16, 14] earlier discharge[17, 18] and decreased likelihood of complications.[15]

In terms of breast surgery, paravertebral blocks have been studied at the breast site mostly after mastectomy. We found two randomized, double-blinded, placebo-controlled trials focused on the mastectomy-only (i.e., no reconstruction) patient population. One of them, by Buckenmaier et al., studied 73 unilateral mastectomy patients and concluded that routine use of a continuous paravertebral block catheter for anesthesia was not supported due to a lack of clinical significance in degree of postoperative pain, nausea, mood state, level of symptom distress, or return to normal activity among the study groups.[19] The second paper, by Moller et al., studied 88 unilateral mastectomy patients with one-time multi-level bupivacaine paravertebral block, but found no statistical difference in pain scores or consumption of analgesics between the study and control groups.[20] We also found one prospective, randomized trial that included patients with lumpectomy and mastectomy.[21] This study by Pusch et al. found that single-injection

paravertebral blocks were quite beneficial and could be used as an alternative to general anesthesia.

We also found two retrospective chart reviews that included tissue expander breast reconstruction patients within their study populations.[22, 23] One of these studies concluded retrospectively that paravertebral blocks in immediate breast reconstruction with tissue expanders may play an important role for decreasing pain and analgesic usage.[22] Overall, these two studies supported the use of paravertebral blocks for analgesia in the breast surgery and breast reconstruction patient population.[21, 22, 23] Additionally, Coopey et al. concluded retrospectively that preoperative paravertebral blocks in patients undergoing mastectomy followed by immediate reconstruction with tissue expanders or implants significantly reduced length of hospital stay, postoperative nausea and shortened the mean time to conversion to oral opioids.[24] Our current proposal is built upon preliminary data gathered from our institution (Table 1). Collectively, patients who received mastectomy-tissue expander reconstruction whom were not offered pre-operative paravertebral block, reported higher incidence of pain complaints during inpatient stay (Table 2). However, we did not find any prospective report focused solely on the use of paravertebral blocks for analgesia in breast reconstruction with tissue expanders, implants or flaps.

Table 1: Number of patients who received pre-operative paravertebral block according to site of breast reconstruction from year 2011-2012

Breast reconstruction site	Paravertebral block (n)	No paravertebral block (n)
Left	9	19
Right	9	18
Bilateral	9	24
Total patients	27	61

Table 2: Analysis of outcome with descriptive statistics

Patient cohorts	Postoperative pain event (P-value)	Duration of inpatient stay (P-value)	Postoperative nausea or vomiting (P-value)
PVB vs non-PVB (Total)	**0.039**	0.17	0.81
PVB vs non-PVB (Unilateral reconstruction)	0.132	0.19	0.75
PVB vs non-PVB (Bilateral reconstruction)	0.423	0.12	0.23

* P-value of <0.05 is considered significant.
PVB = Paravertebral block

Moreover, to date, we do not know of any prospective, randomized placebo-controlled trials reported in tissue expander-based breast reconstruction patients. In fact, the PSEF Device and Technique Assessment (DATA) committee issued a call for prospective, randomized implanted bupivacaine pain pump studies in 2006.[25] We believe, therefore, that prospective, randomized, double blind trials are still warranted to confirm the efficacy and safety of continuous bupivacaine infusion via a pain pump in plastic surgery patients. The innovation of

our study is that paravertebral blocks are similar in philosophy to the pain pumps, but less expensive and with lower risk of infection.

We hypothesize that post-operative static pain scores will be lower in ropivacaine patients vs. placebo patients in women undergoing bilateral mastectomy and bilateral immediate reconstruction with placement of tissue expanders. We believe that post-operative moving pain scores, opioids use, nausea, and sleep interference will be likewise improved. We further hypothesize that this decreased post-operative pain may lead to improvements in long-term health outcomes as measured by validated questionnaires. In the presence of clear need and lack of published studies regarding this precise patient population, it is important to determine if paravertebral blocks do reduce post-operative pain, and improve opioids use, nausea, sleep interference, and length of hospital stay in patients undergoing immediate tissue expander breast reconstruction.

4. Objectives

4.1 Primary Objective

To determine if post-operative static pain scores differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

4.2 Secondary Objectives

To determine if post-operative moving pain scores, opioid use, nausea, sleep interference, and length of hospital stay differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

4.3 Tertiary Objectives

To determine if long-term changes in Quality of Life scores [(the RAND-36 Health Survey, Disability of the Arm, Shoulder, and Hand (Quick DASH) questionnaire, and Breast-Q scores)] differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

5. Investigational Plan

5.1 Summary of Study Design

Participants meeting inclusion criteria will be enrolled and baseline data collection completed prior to randomization and surgery. Baseline data collection includes a general patient history, the Patient Pain Assessment Questionnaire which includes static and moving pain scores as well as nausea and sleep interference scores (Appendix A), the Subjective Pain Survey (Appendix B), the pre-operative Breast-Q (Appendix C), the RAND-36 (Appendix E), and the Quick DASH survey (Appendix F).

Patients will be randomized 1:1 to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections in a double-blinded design. Neither the treatment team (the anesthesiologist and the surgeon) nor the patient will know the randomization assignment. The pharmacy will be unmasked.

Patient-specific surgical details will be recorded intraoperatively. Following the surgery, post-operative pain [(measured by the Patient Pain Assessment Questionnaire (Appendix A)], pain medication/opioid use, and the occurrence of adverse events (AEs)/serious adverse events (SAEs) will be assessed routinely by staff during the hospital stay and on Days 2 and 3 by telephone interview with study staff for discharged patients. The typical post-operative length of hospital stay is approximately one day. Participants are to return to clinic for the Day 7 (±2 days) follow-up visit. At this visit an updated medical history will be completed, pain medication/opioid use recorded, and participant AEs/SAEs assessed. Additionally, participants will complete the following questionnaires: Patient Pain Assessment, RAND-36, and Quick DASH.

Long-term quality-of-life/health outcomes assessments will be done on post-operative Day 90 (±14 days), Year 2 (±14 days), and Year 4 (±14 days). During the Day 90 visit, pain scores (Patient Pain Assessment Questionnaire), pain medication/opioid use, post-operative Breast-Q, RAND-36, and the Quick DASH will be administered. The Year 2 and Year 4 follow-ups are included as tertiary endpoints to capture differences in chronic pain, and patients will be asked to complete the same questionnaires as at the Day 90 follow up.

5.2 Patient Population

All patients presenting to the Johns Hopkins Avon Foundation Breast Center for surgical management of high risk for breast cancer, pre-malignant breast lesions, or breast cancer leading to bilateral mastectomies with reconstruction will be evaluated for participation. Those meeting inclusion criteria and no exclusion criteria may be enrolled into the study.

5.2.1 Inclusion Criteria

Eligible participants must

- Be Female aged 18-100 years.
- Choose bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction.
- Have no inflammatory breast cancers.
- Be aware of the nature of her malignancy.
- Understand the study purpose, requirements, and risks.
- Be able and willing to give informed consent.

5.2.2 Exclusion Criteria

Participants with the following conditions will be ineligible:

- Any concurrent opioid analgesic use (baseline opioid use must be 0 to be eligible).
- Liver dysfunction and/ or cirrhosis.

- Renal insufficiency, with creatinine greater than 1.5 mg/mL.
- Patients weighing less than 50 Kg.
- Concurrent use of the SSRI antidepressant fluvoxamine (Luvox).

Having a tattoo on the back that is too large to permit PVB injections (as determined by the provider performing the procedure).

5.3 Inclusion of Women and Minorities

This study is open to accrual of women only. Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined.

5.4 Determination of Eligibility

Potential subjects will be consented by the study investigators or study staff. If determined eligible, subjects will be registered with the study coordinator through the assignment of a study-specific ID number.

5.5 Randomization

During the study, patients desiring a bilateral mastectomy followed by bilateral immediate tissue expander reconstruction will be randomized to ropivacaine- pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections at the same site as the paravertebral block. Randomization will be performed by the pharmacy when the medication is requested prior to paravertebral block administration.

A master list of randomization assignments made by the protocol biostatistician will be delivered to the Research Pharmacy at Johns Hopkins. Other key personnel may also receive this list, if required.

5.6 Blinding

Both patients and the treating anesthesiologist(s) will be blinded as to whether the patients are receiving a ropivacaine (treatment) or saline (placebo) solution through the Day 90 visit. One anesthesiologist (who is also a co-investigator), which will not be involved with the intra- and postoperative patient care and data collection, will perform all the paravertebral blocks and sham procedures. The anesthesiologists managing intra- and postoperative patient care and all data collection will be unaware of the group assignment. Postoperative assessments will be performed by anesthesiologists who will be blinded to each patient's group. This strategy will allow a double-blinded design. Blinding the study will help to reduce the chance of bias in subjective outcomes such as pain scores and quality-of-life scores. Once all enrolled patients have completed their Day 90 visit, unblinding will occur for study staff to enable data analysis. Patients will have the option of learning their treatment assignment group once they have completed their Year 4 follow-up interview.

In case of an emergency when the treating investigator deems identification of the study drug necessary for the purpose of providing urgent patient care, and knowledge of the subject's treatment assignment will alter subsequent care, then the investigator is authorized to break the blind. In order to learn of the randomization assignment, the Principal Investigator or designee will contact the Research Pharmacy to request treatment assignment information.

5.7 Treatment Administration

The randomized treatment assignment will be prepared by the pharmacy. Upon arrival to the operating room, standard vital sign monitors will be placed and the patient will be positioned in the sitting position. After administering light sedation with low-dose midazolam and fentanyl, the skin of the back will be cleaned with chlorhexidine antiseptic. Local anesthesia of the skin, subcutaneous tissue and periosteum of the transverse processes 2.5-cm lateral to each side of the thoracic spine (T2-T8) will be performed using 2–5 ml of lidocaine 10 mg/ml. The paravertebral block injections of study solution will occur using the landmark-based classic or ultrasound-guided technique with a 22-guage Tuohy needle. Double-blinding of patients (study subjects) and physicians/the study team will be maintained, unless it becomes critically necessary to break double-blinding randomization for medical care. One-half of patients will get subcutaneous injectable normal saline (3 to 5 mL at each of 14 injections sites), and one-half will get 0.5% ropivacaine (up to 0.8 mL/kg, equivalent to 4mg/kg). Immediately after completion of the paravertebral injections or subcutaneous injections, the patients will be repositioned supine and general anesthesia induced in the standard manner. All patients will also receive Fentanyl 1.5 mcg/kg 5-10 minutes prior to surgical incision. The primary anesthesia team in the operating room caring for the patient will not be involved in preparation, randomization, or block placement.

The standard orders for the PCA pump and opioid are per the currently used Sunrise POE order set for plastic surgery patients. No changes will be made to the standard administration of anesthesia or to currently available postoperative orders.

5.8 Justification For Placebo

In clinical trials of surgical interventions, sham procedure is an important scientific control. The sham paravertebral subcutaneous saline injections will contribute to isolate the specific effects of the treatment drug (ropivacaine hcl) as opposed to the patient's perception of having had a regular paravertebral block. Thus, sham paravertebral subcutaneous saline injections serve an analogous purpose to placebo drugs, neutralizing biases such as the placebo effect. Additionally, the subcutaneous paravertebral injections of placebo (normal saline) do not carry increased risks besides the potential risks of the injection process itself. The potential risks associated with the injection process itself include the risk of inadvertent vascular puncture (6.8%), pleural puncture (0.8%) and pneumothorax (0.5%),[26] all of which are classified as unlikely events (occurring in 1-10 of every 100 patients). Hence, the administration of placebo will strengthen the study design and any conclusion reached without significantly increasing the risk of complications.

5.9 Dose Modifications

The administration of the blocks will be ceased if the patient is experiencing any unanticipated adverse events (i.e., worse side effects than predicted). (See section 7.1.7 for potential side effects.)

5.10 Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the medical records and followed up through the Day 7 post-operative visit.

5.11 Duration of Study Participation

Study participation continues through Year 4 post-operatively. However, the majority of data collection will occur during the first 7 days after the participant's immediate tissue expander reconstruction following mastectomy. An additional study visit will occur in clinic at Day 90 (±14 days), prior to the participant's undergoing any additional reconstructive breast surgery procedures. Thereafter, follow-up phone interviews will occur at post-operative Year 2 (±14 days), and post-operative Year 4 (±14 days).

Participants are to return to clinic for a Day 90 (±14 days) follow-up visit. To encourage participation, participant parking and a $15 gift card will be given (or mailed) to participants who complete the Day 90 visit.

If a participant chooses to withdraw, is withdrawn, or refuses to participate through Day 90, all efforts will be made to collect all Day 90 post-operative data at the time of study withdrawal. Reasons for premature participation/treatment withdrawal will be recorded to the best of the study team's ability. Reasons for early withdrawal may include the following:

1. Unanticipated or serious adverse events.
2. Inter-current illness that prevents further administration of treatment or would affect assessment of clinical status to a significant degree.
3. Subject becomes pregnant.
4. Subject refuses to continue treatment.
5. Any reason the study physician deems it necessary for the benefit of the participant.
6. Subject is lost to follow-up.

6. Study Calendar

Table 3. Calendar of study events/procedures.

Parameter	Pre-Study	Surgery (Day 0)	Day1	Day 2*	Day 3*	Day 7 (±2 days)	Day 90 (±14 days)	Post-Op Years 2 & 4 (±14 days)
General Patient History Form	X							
Update Medical History		X	X			X	X	X
Treatment administration (Ropivacaine/Placebo)		X						
Intra-Operative Case report Form (CRF)		X						
Adverse Events of Interest/SAE Assessment		X	X	X	X	X	X	
Pain Meds/Opioid Use	X		X	X	X	X	X	
Questionnaires								
Patient Pain Assessment Questionnaire	X		X	X	X	X	X	X

Subjective Pain Survey	X							
BREAST-Q©, Pre-Op	X							
BREAST-Q©, Post-Op							X	X
RAND-36 Questionnaire	X					X	X	X
Quick DASH Questionnaire	X					X	X	X

Note: Additional tests may be performed at the discretion of the treating investigator as clinically indicated.

* A study team member will call discharged patients on Day 2 and Day 3 to collect data. Phone calls will not occur on weekends but will resume the following Monday. If the patient is not discharged, study follow-up will occur at bedside.

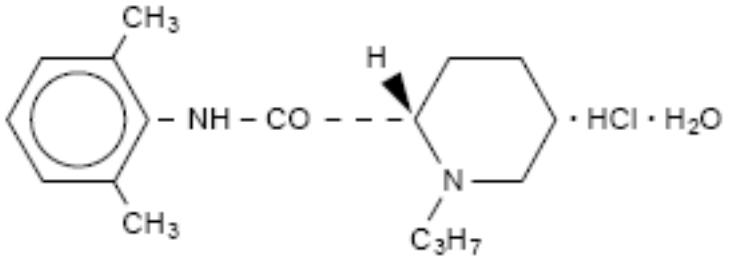
7. Pharmaceutical Information

7.1 Ropivacaine (Naropin®)

7.1.1 Product Identification

Naropin® injection contains ropivacaine HCl, which is a member of the amino amide class of local anesthetics. Naropin® (ropivacaine HCl) injection is a sterile, isotonic solution that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and water for injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. It is administered parenterally.

Ropivacaine HCl is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a molecular formula of $C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$, molecular weight of 328.89 and the following structural formula:



At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Naropin (ropivacaine hcl) Injection is preservative-free and is available in single dose containers in 2 (0.2%), 5 (0.5%), 7.5 (0.75%) and 10 mg/mL (1%) concentrations. The specific gravity of Naropin (ropivacaine hcl) Injection solutions range from 1.002 to 1.005 at 25°C.

7.1.2 Mode of Action

A) MECHANISM OF ACTION

1) Local anesthetics bind to the internal axoplasmic membrane (presumably a phospholipid receptor) to reduce ion flux, especially the sodium channel, resulting in inhibition of depolarization and subsequent nerve conduction blockade. Ropivacaine may have a greater propensity for blocking small myelinated A fibers and nonmyelinated C fibers (pain fibers) than bupivacaine; sensory blockade with ropivacaine is generally more pronounced than motor blockade, and the intensity and duration of motor block is lower and shorter with ropivacaine than with equal doses of bupivacaine.

a) With single injections of high concentrations of ropivacaine for epidural analgesia, motor blockade was dose-dependent in segments close to the injection site (L2/3); in abdominal muscles, the blockade was partial and not clearly correlated with ropivacaine concentration.

b) For epidural analgesia, ropivacaine infused continuously at a 0.1% concentration produced motor blockage so slight that all study subjects could be mobilized; at 0.2% and 0.3% concentrations of ropivacaine infusion, blockade was moderate (40% to 50% of baseline force was present).

B) PHARMACOLOGY

1) Ropivacaine is a long-acting amino-amide local anesthetic with pharmacodynamic properties and uses similar to those of bupivacaine. The S-(-)-enantiomer of 1-propyl-2,6-pipecoloxylidide, ropivacaine is structurally similar to bupivacaine and mepivacaine. The S-(-) and R-(+) enantiomers of ropivacaine are equipotent in terms of local anesthetic effects; however, nerve block with the S-(-) isomer is slightly longer, and toxicity appears to be less. In contrast to ropivacaine, both bupivacaine and mepivacaine are available as racemic mixtures.

2) Bupivacaine is considered more cardiotoxic than other amide-type local anesthetics, and this is attributed to its R-(-) isomer. Ropivacaine was developed to be a less toxic alternative to bupivacaine. In addition to its availability in the S-isomeric form, ropivacaine differs from bupivacaine by substitution of the butyl group by a propyl group; these changes make ropivacaine less lipid soluble and potentially less likely to induce cardiotoxic effects.

3) In vitro and in vivo studies have suggested a similar anesthetic profile with bupivacaine and ropivacaine, but a greater potential for central nervous system toxicity and cardiotoxicity with the former when given in equal doses (milligram-basis);

ropivacaine may have a greater margin of safety between convulsive and lethal doses. Ropivacaine was less likely than bupivacaine to produce mild cardiovascular and central nervous system changes after intravenous infusion in one study involving healthy subjects. The intensity and duration of motor blockade have tended to be less with epidural ropivacaine compared to epidural bupivacaine.

4) Ropivacaine has vasoconstrictor properties. The drug has produced significant blanching and reduced cutaneous blood flow when infiltrated. The addition of epinephrine may not measurably decrease drug absorption or prolong the duration of blockade of ropivacaine.

7.1.3 Storage and Stability

Store solutions at 15-30°C.

Do not freeze. Due to the nature of the Polyamp® and the Polybag® systems, the containers must not be re-autoclaved.

NAROPIN (ropivacaine hydrochloride) solutions are sterile, without preservative and are for single use only. Discard unused portion.

7.1.4 Indications

NAROPIN (ropivacaine hydrochloride) is indicated for:

Analgesia

Acute pain management in connection with:

- Continuous epidural infusion or intermittent bolus administration e.g., postoperative or labour pain;
- Field block e.g. infiltration.

Anaesthesia

Surgical anaesthesia in connection with:

- Epidural block for surgery, including Caesarean section;
- Major nerve block e.g., brachial plexus block;
- Field block e.g., infiltration.

7.1.5 Contraindications

NAROPIN (ropivacaine hydrochloride) is contraindicated:

- In patients with a hypersensitivity to ropivacaine or any other local anaesthetic agent of the amide type;
- For intravenous regional anaesthesia (Bier block);
- In obstetric paracervical block anaesthesia. Use of other local anaesthetics in this technique has resulted in foetal bradycardia and death.

7.1.6 Availability

Absorption: The systemic concentration of local anaesthetics is dependent upon the total dose and the concentration administered, the route of administration, the patient's hemodynamic/ circulatory condition, and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space. The mean half-lives of the two phases are in the order of 14 min and 4 h. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose proportionality at epidural doses up to 250 mg and intravenous doses up to 80 mg.

Distribution: Following intravenous administration, the volume of distribution of NAROPIN is approximately 40 L. NAROPIN is extensively bound to alpha1-acid glycoprotein in plasma with an unbound, i.e. pharmacologically active, fraction of about 6%. An increase in total plasma concentration during continuous epidural infusion has been observed in postoperative patients and is related to the postoperative increase of alpha1-acid glycoprotein. Variations in unbound concentration have been much less than in total plasma concentration.

Ropivacaine readily crosses the placenta and equilibrium, in regard to unbound concentration, is rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus than in the mother. The ratios of umbilical vein to maternal vein total and free concentrations are 0.31 and 0.74, respectively.

Metabolism: Ropivacaine is extensively metabolized in the liver predominantly to 3- hydroxy-ropivacaine by an aromatic hydroxylation process mediated by cytochrome P4501A2 and N-dealkylation to PPX mediated by CYP3A4. Conjugated and unconjugated 3-hydroxy-ropivacaine represent the major urinary metabolites. Urinary excretion of 4-hydroxy ropivacaine, N-dealkylated pipecoloxylidide (S-PPX) and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites account for less than 3% of the dose. An additional metabolite, 2- hydroxy-methyl-ropivacaine has been identified, but not quantified in urine. S-PPX and 3- hydroxy ropivacaine are the major metabolites excreted in the urine during epidural infusion. A total S-PPX concentration in the plasma was about half that of total ropivacaine however, mean unbound concentrations of S-PPX were about 7 – 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. The threshold for CNS toxicity in rats due to unbound plasma concentrations of PPX is approximately 12 times higher than that of unbound ropivacaine. S-PPX, 3-hydroxy ropivacaine, and 4-hydroxy ropivacaine have a pharmacological activity in animal models less than that of ropivacaine.

There is no evidence of in vivo racemization of ropivacaine.

Excretion: After intravascular administration, 86% of the total dose of ropivacaine is excreted in the urine of which approximately 1% is the parent compound and 36% is 3- hydroxy-ropivacaine. Ropivacaine has a mean total plasma clearance in the order of 440 mL/min, an unbound plasma clearance of 8 L/min, a renal clearance of 1 mL/min, and a volume of distribution at steady state of 47 L. Ropivacaine has an intermediate hepatic extraction ratio of

about 0.4. The terminal elimination half-life is 1.6 to 1.8 hours after intravenous administration, 4.1-6.5 hours after epidural administration, and 5.7-8.0 hours after brachial plexus block. The total and unbound clearance of epidural ropivacaine at term in pregnancy (223-256 mL/min and 2.8-3.3 L/min, respectively), are lower than that observed in non-pregnant patients.

7.1.7 Side Effects

Reactions to NAROPIN (ropivacaine hydrochloride) are characteristic of those associated with other long-acting local anesthetics of the amide type.

In clinical trials, the great majority of adverse events reported with ropivacaine were related to the expected effects of the block and to the clinical situation, rather than reactions to the drug.

When all clinical studies were pooled (total n=3056), hypotension and nausea were registered in 41.2% (n=1259) and 28.4% (n=867) of the patients, respectively. Similar incidences were reported for bupivacaine in the double-blind comparisons.

Adverse reactions to local anesthetics are very rare in the absence of overdose or inadvertent intravascular injection. The effects of systemic overdose and unintentional intravascular injections can be serious, but should be distinguished from the physiological effects of the nerve block itself (e.g. a decrease in blood pressure, bradycardia, urinary retention after epidural and intrathecal block), and events caused directly by needle puncture (e.g. spinal haematoma, postdural puncture headache), or indirectly by introduction of micro-organisms (e.g. meningitis and epidural abscess).

Acute systemic toxicity from local anaesthetics is generally dose-related and due to high plasma levels which may result from overdosage (see OVERDOSAGE), rapid absorption from the injection site, diminished tolerance, or from inadvertent intravascular injection. Most commonly, the acute adverse experiences originate from the central nervous and cardiovascular systems.

7.1.8 Overdosage

Systemic toxic reactions primarily involve the central nervous system and cardiovascular system. Such reactions are caused by high plasma levels encountered during therapeutic use, overdose, or to unintended intravascular or subarachnoid injection (see ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS). CNS reactions are similar for all amide local anesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Symptoms
Accidental intravascular injections may cause immediate (within seconds to a few minutes) toxic effects. In the event of overdose, peak plasma concentrations may not be reached for 1 to 2 hours, depending on the site of injection, with signs of toxicity thus being delayed.
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. First symptoms are usually light-headedness, circumoral paraesthesia, numbness of the

tongue, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalized convulsions. These signs must not be mistaken for a neurotic behavior. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases apnea may occur. Acidosis, hyperkalemia, hypocalcemia and hypoxia increase and extend the toxic effects of local anesthetics.

Recovery is due to redistribution and metabolism of the local anesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular system toxicity indicates a more severe situation and is generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations of local anesthetic. In volunteers, the intravenous infusion of ropivacaine resulted in signs of depression of conductivity and contractility.

In children early signs of local anesthetic toxicity may be difficult to detect in cases where the block is given during general anesthesia. It should be noted that NAROPIN (ropivacaine hydrochloride) is not approved for use in pediatric patients.

Treatment
The first consideration is prevention, best accomplished by incremental injection of NAROPIN, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered. If signs of acute systemic toxicity appear, injection of the local anesthetic should be immediately stopped.

The first step in the management of systemic toxic reactions, as well as hypoventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask and bag or tracheal intubation. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control the convulsions. An anticonvulsant should be given i.v. if the convulsions do not stop spontaneously in 15-20 seconds. Thiopental 1–3 mg/kg i.v. will abort the convulsions rapidly. Alternatively, diazepam 0.1 mg/kg i.v. may be used, although its action will be slow. Both these drugs, however, depress the central nervous system, respiratory and cardiac functions, add to postictal depression, and may result in apnea.

Prolonged convulsions may jeopardize the patient's ventilation and oxygenation. If so, injection of a muscle relaxant such as succinylcholine (1 mg/kg) will stop the muscle convulsions rapidly,

so that ventilation and oxygenation can be controlled. Endo-tracheal intubation must be considered in such situations.
If cardiovascular depression is evident (hypotension, bradycardia) administration of intravenous fluids or a vasopressor such as ephedrine or epinephrine may be required.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the likelihood of a successful outcome.

Clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen, which may avoid cardiac arrest.

In human volunteers given intravenous NAROPIN, the mean maximum tolerated total and free arterial plasma concentrations were 4.3 and 0.6 μg/mL respectively, at which time moderate CNS symptoms (muscle twitching) were noted.

7.2 Placebo

Patients randomized to the placebo group will be administered 0.9% sodium chloride solution at a dose of 0.8 mL/kg, using the technique described in the treatment administration section (section 5.7).

7.3 Opioid use

Other opioid use such as IV PCA (morphine) and PO opioids (oxycodone) will be standardized by conversion into morphine equivalents based on a 24-hour regimen using Table 4.

Table 4. Standardization table for Opioid use by participants based on the "Equianalgesic Dosing of Opioids for Pain Management*."

Morphine (mg/day)		**Oxycodone** (mg/day)	
Oral	IV	Oral	IV
45-134	8-22	22.5-67	12-33
135-224	23-37	67.5-112	33.1-56
225-314	38-52	112.5-157	56.1-78
315-404	53-67	157.5-202	78.1-101
405-494	68-82	202.5-247	101.1-123
495-584	83-97	247.5-292	123.1-147
585-674	98-112	292.5-337	147.1-168
675-764	113-127	337.5-382	168.1-191
765-854	128-142	382.5-427	191.1-213
855-944	143-157	427.5-472	213.1-236
945-1034	158-172	472.5-517	236.1-258
1035-1124	173-187	517.5-562	258.1-281

*http://pharmacy.uams.edu/formulary/narc_conv_chart.htm

8. Administrative Procedures

8.1 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB prior to implementation.

8.2 Informed Consent

The investigator or other qualified study team member will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration of study participation, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. No subject will enter the study before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

8.3 Ethics and Good Clinical Practice

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in the following:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described herein and, thereby, to adhere to the principles of Good Clinical Practice to which it conforms.

9. Adverse Events

9.1 General

This study is collecting data regarding post-operative pain after a planned surgical procedure. The placement of the paravertebral block and ropivacaine is not expected to cause increased side effects or problems than those already anticipated with surgery. Subjects randomized to the placebo group will be at increased risk of harm related to the subcutaneous paravertebral saline injections without the chance of benefit. Any events that occur that are deemed "unexpected" to

the surgical procedure(s) performed, but related to the study procedures will be reported per current institutional requirements.

9.2 Definitions

9.2.1 Adverse Event (AE)

Any undesirable sign, symptom or medical condition occurring after starting study drug (even if the event is not considered to be related to the study) is considered an adverse event. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form will be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

9.2.2 Serious Adverse Event or Reaction

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Required or prolonged hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or a birth defect;
- Is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition, or for elective procedures (i.e., venous access placement, etc.).
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.2.3 Expectedness

9.2.3.1 Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

9.2.3.2 Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

9.3 Relationship

The relationship of all adverse events and serious adverse events to study medication will be assessed by an investigator and assigned as follows:

9.3.1 Definitely: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, and for which no alternative cause is present.

9.3.2 Probably: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, but for which a potential alternative cause may be present.

9.3.3 Possibly: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, but a potential alternative cause does not exist.

9.3.4 Unlikely: An adverse event which does not have a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational drug/agent.

9.3.5 Unrelated: An adverse event for which there is evidence that it is definitely related to a cause other than the investigational drug/agent. In general, there is no timely relationship to the administration of the investigational drug/agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

9.4 Reporting Procedures

9.4.1 General

All adverse events will be captured on the appropriate study-specific case report forms (CRFs). In addition, all serious adverse events, regardless of causality to study drug, will be reported promptly to the Principal Investigator and Study Coordinator.

9.4.2 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the study protocol and informed consent, these modifications will be provided to the IRB with the report of the adverse event or as soon as possible thereafter.

9.4.3 Food and Drug Administration (FDA)

In this trial using a medication for an FDA-approved indication, unexpected adverse events believed to be definitely, probably, or possibly related to the medication (s) will be reported to the Food and Drug Administration via Med Watch (using the online form available at https://www.accessdata.fda.gov/scripts/medwatch/; by telephone 1-800-FDA-1088; or by fax 1-800-FDA-0178 using form available at http://www.fda.gov/medwatch/report/hcp.htm). This reporting mechanism will be used to report events that may be related to the use of the ropivacaine.

9.5 Data and Safety Monitoring

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan. The Clinical Research Office QA Group will perform an audit at the end of the first year and then periodically depending on the rate of accrual and prior audit results. The SKCCC Safety Monitoring Committee will review all trial monitoring and reporting annually. The PI will be responsible for monitoring the study. The study's data will be continuously reviewed to assure its validity. The PI will constantly review the safety reports to confirm that the safety outcomes favor continuation of the study. Additionally, the PI will be responsible for maintaining the clinical protocol, monitoring clinical trial efficacy endpoints, reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the continuing renewal report submitted to the IRB and to the trial monitoring review group.

Content of the continuing renewal report at a minimum will include year-to-date and full trial data on: accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR reports, response, survival, regulatory compliance and compliance with prearranged statistical goals. The report will be submitted in a timely manner according to the schedule defined by Johns Hopkins Medicine Institutional Review Board.

9.6 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. The Principal Investigator as well as the Sidney Kimmel Comprehensive Cancer Center Clinical Research Office will review these data for completeness and accuracy.

9.7 Safety Meetings

Scheduled meetings will take place as needed and will include the protocol principal investigator, study coordinator(s), sub-investigators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants,

adherence to the protocol (i.e., potential or real protocol deviations/violations), completeness of data collection, and progress of data analysis.

9.8 Monitoring

The principal investigator will have sole responsibility for monitoring and oversight of problems/events related to this research.

10. Statistical Considerations

This study is a randomized controlled trial based on the bilateral mastectomy followed by bilateral immediate tissue expander breast reconstruction surgical protocol currently in use at Johns Hopkins.

Patients will be randomized 1:1 to either 0.5% ropivacaine pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections. Using two pain scales, the Patient Pain Assessment Questionnaire (Appendix A) and Subjective Pain Survey (Appendix B), the post-operative pain will be compared between treatment and control groups. Differences in opioids use between groups at different time points will also be assessed as a more objective measure of post-operative pain.

10.1 Objectives

10.1.1 Primary Objective

To determine if post-operative static pain scores differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

Post-operative pain scores will be measured by a 0-10 Likert scale 6 hours after the end of surgery while the patient is still hospitalized (post-operative day 0). This will be patient-provided data. Unblinded data analysis will compare scores between treatment and control groups.

10.1.2 Secondary Objectives

To determine if post-operative moving pain scores, opioids use, nausea, and sleep interference differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

Pain score, opioids use, nausea, and sleep interference data will be collected via patient self-report. When possible (i.e., while hospitalized) objective data on opioids and other pain medication administered to the patient will be used.

10.1.3 **Tertiary Objectives**

To determine if long-term changes in Quality of Life scores [the RAND-36 Health Survey, Disability of the Arm, Shoulder, and Hand (Quick DASH) questionnaire, and Breast-Q scores] differ between women undergoing bilateral mastectomy followed by bilateral immediate tissue expander reconstruction randomized either to ropivacaine- (treatment) pre-operatively placed paravertebral blocks or subcutaneous paravertebral saline (placebo) injections.

This data will be collected via validated questionnaires through patient interviews at 3-months, 2-years, and 4-years (±14 days) after surgery.

Once enrolled in the study, participants will be encouraged to remain in the study for the 4 years following surgery in order to get final pain scores and quality-of-life/health outcome survey information. Participants who cannot be contacted after several phone attempts and the sending of 2 certified letters via US Postal Service for 3-month, 2-year, and/or 4-year outcome assessments will be considered lost to follow-up.

10.2 Study Design

Descriptive statistics for all outcome data (primary, secondary, and tertiary) will be calculated for each treatment group (ropivacaine or placebo), for each time point (days 1-3, day 90, year 2 and year 4). Student's t-test or Wilcoxon rank sum test will be used to compare the 2 treatment groups with regards to continuous or ordinal (approximately continuous) data, based on the distribution of the values (normally distributed or not normally distributed). Also change from baseline to each time point (follow-up) will be calculated for each outcome. The distributions of these "change values" will be analyzed in the same manner (depending on distribution). P-values less than 0.05 will be considered statistically significant for the primary outcome.

Longitudinal methods will be used to examine trends in scores, and changes in scores over time.

Opioid use also will be analyzed. IV morphine delivered via a Patient Controlled Analgesia pump during the first 24 hours of post-operative hospitalization will be recorded. Oxycodone and Tylenol taken by the patient after the first 24 hours until post-operative day seven will be recorded by the patient unless the patient is still hospitalized, in which case it will be recorded in the patient's medical record and abstracted by study staff. Answers to pain questionnaires and information regarding analgesic use will be verified by daily telephone calls to the patients by study staff. A common "pain unit" will be developed to standardize the various methods of opioid administration. Survival analyses will be used to compare time to opioid use, and time to stopping of opioid use. Descriptive statistics will be used to quantify amount and timing of opioid use, as well as proportion of patients requiring opioids post-operatively.

Furthermore, we will use the DASH survey, BREAST-Q©, and the RAND-36 to determine the amount of functional long-term differences (3 months, 2 and 4 years after surgery) between treatment groups. These surveys will be used to compare the functional use of the arm before surgery to its use three months after mastectomy with immediate reconstruction.

Adverse events will be quantified and proportions of patients in each treatment group with different specific types of adverse events will be compared for safety data. Chi Square tests or Fisher's Exact Tests will be used to compare the proportions of patients with adverse events.

10.3 Sample Size and Accrual

We expect that it will take 24 months to collect data on all patients through Day 90. Assuming a placebo effect of 30%, we would anticipate a true difference of 1.5 VAS units between the two groups. A true difference between scores of 4.1 to 2.6 would be clinically significant since it would bring a patient from the "moderate" down into the "mild" pain category. Thus a total of 70 patients will enter this placebo-control parallel-design study. The probability is 90 percent that the study will detect a treatment difference at a two-sided 0.05 significance level. This is based on the assumption that the standard deviation of the response variable is 2.5.

10.4 Interim Analyses for Efficacy.

A total of two interim analyses for efficacy will occur after the enrollment of 28 (40%) and 42 (60%) patients, giving a total of 3 'looks' at the data including the final analysis at 70 patients enrolled. Because of the small sample size in the first and second interim analyses, we will test for the equality of static pain scores at 6 hours post-surgery by treatment group using the Wilcoxon rank sum test. This statistical test considers the rank of the pain scores without regard to the distribution of these outcome measures; however, the test of significance uses a Z-score, which has a standard normal distribution.

In order to control for the overall type I error for the three proposed analyses, we will use a group sequential approached that utilizes the O'Brien-Fleming (1979)[27] alpha spending function. The critical Z-values for the Wilcoxon rank sum test assuming O'Brien-Fleming boundaries were determined by the STATA command 'landemets', which calculates these boundaries following the method of Lan and DeMets (1983)[28]. Table X below gives the critical Z values and corresponding alpha levels at each analysis required to reject the null hypotheses of equality of pain scores by treatment group. In this null hypothesis, we consider a two-sided test which makes no assumption about the direction of the effect (e.g. placebo patients could potentially have a lower mean pain score than those on the intervention).

Table 5: Critical Z values and corresponding alpha levels for test the null hypothesis that static 6 hour post-surgery pain scores are equal among treatment groups.

Analysis number	Proportion of total N	critical |Z| to reject H0	Alpha(i) level
1	0.4	3.36	0.00079
2	0.6	2.68	0.0076
3	1.0	1.98	0.05

References

1. Al-Ghazal SK, Sully L, Fallowfield L, Blamey RW. The psychological impact of immediate rather than delayed breast reconstruction. Eur J Surg Oncol 2000;26:17-9.
2. Cocquyt VF, Blondeel PN, Depypere HT, et al. Better cosmetic results and comparable quality of life after skin-sparing mastectomy and immediate autologous breast reconstruction compared to breast conservative treatment. Br J Plast Surg 2003;56:462-70.
3. Khoo A, Kroll SS, Reece GP, et al. A comparison of resource costs of immediate and delayed breast reconstruction. Plast Reconstr Surg 1998;101:964-8; discussion 9-70.
4. Alderman AK, McMahon L, Jr., Wilkins EG. The national utilization of immediate and early delayed breast reconstruction and the effect of sociodemographic factors. Plast Reconstr Surg 2003;111:695-703; discussion 4-5.
5. Rosson GD, Singh NK, Ahuja N, Jacobs LK, Chang DC. Multilevel analysis of the impact of community vs patient factors on access to immediate breast reconstruction following mastectomy in Maryland. Arch Surg 2008;143:1076-81; discusion 81.
6. Wilkins EG, Cederna PS, Lowery JC, et al. Prospective analysis of psychosocial outcomes in breast reconstruction: one-year postoperative results from the Michigan Breast Reconstruction Outcome Study. Plast Reconstr Surg 2000;106:1014-25; discussion 26-7.
7. Legeby M, Segerdahl M, Sandelin K, Wickman M, Ostman K, Olofsson C. Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain. Breast 2002;11:156-62.
8. Legeby M, Sandelin K, Wickman M, Olofsson C. Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction. Acta Anaesthesiol Scand 2005;49:1360-6.
9. Naja Z, Al Tannir M, Naccache N, El Rajab M, Al Sayyid K, Ziade F, Chatila M. General anaesthesia combined with bilateral paravertebral blockade (T11-T12-L1) vs general anaesthesia for bilateral varicocelectomy. A randomized double-blind clinical trial. J Med Liban. 2011 Jul-Sep;59(3):126-30.
10. Kaya FN, Turker G, Basagan-Mogol E, Goren S, Bayram S, Gebitekin C. Preoperative multiple-injection thoracic paravertebral blocks reduce postoperative pain and analgesic requirements after video-assisted thoracic surgery. JCardiothorac Vasc Anesth. 2006 Oct;20(5):639-43. Epub 2006 Aug 8.
11. Moussa AA. Opioid saving strategy: bilateral single-site thoracic paravertebral block in right lobe donor hepatectomy. Middle East J Anesthesiol. 2008 Feb;19(4):789-801.
12. Chelly JE, Ploskanych T, Dai F, Nelson JB. Multimodal analgesic approach incorporating paravertebral blocks for open radical retropubic prostatectomy: a randomized double-blind placebo-controlled study. Can J Anaesth. 2011 Apr;58(4):371-8. Epub 2010 Dec 21.
13. Fibla JJ, Molins L, Mier JM, Sierra A, Carranza D, Vidal G. The efficacy of paravertebral block using a catheter technique for postoperative analgesia in thoracoscopic surgery: a randomized trial. Eur J Cardiothorac Surg. 2011 Oct;40(4):907-11. Epub 2011 Feb 11.
14. Splinter WM, Thomson ME. Somatic paravertebral block decreases opioid requirements in children undergoing appendectomy. Can J Anaesth. 2010 Mar;57(3):206-10. Epub 2010 Jan 9.

15. Kaya FN, Turker G, Mogol EB, Bayraktar S. Thoracic paravertebral block for video-assisted thoracoscopic surgery: single injection versus multiple injections.J Cardiothorac Vasc Anesth. 2012 Feb;26(1):90-4. Epub 2011 Nov 4.
16. Tug R, Ozcengiz D, Güneş Y. Single level paravertebral versus caudal block in paediatric inguinal surgery.Anaesth Intensive Care. 2011 Sep;39(5):909-13.
17. Naja ZM, El-Rajab M, Ziade F, Al-Tannir M, Itani T. Preoperative vs. postoperative bilateral paravertebral blocks for laparoscopic cholecystectomy: a prospective randomized clinical trial.Pain Pract. 2011 Nov-Dec;11(6):509-15. doi: 10.1111/j.1533-2500.2011.00447.x. Epub 2011 Mar 30.
18. Naja MZ, Ziade MF, Lönnqvist PA. General anaesthesia combined with bilateral paravertebral blockade (T5-6) vs. general anaesthesia for laparoscopic cholecystectomy: a prospective, randomized clinical trial.Eur J Anaesthesiol. 2004 Jun;21(6):489-95.
19. Buckenmaier CC 3rd, Kwon KH, Howard RS, McKnight GM, Shriver CD, Fritz WT, Garguilo GA, Joltes KH, Stojadinovic A. Double-blinded, placebo-controlled, prospective randomized trial evaluating the efficacy of paravertebral block with and without continuous paravertebral block analgesia in outpatient breast cancer surgery. Pain Med. 2010 May;11(5):790-9.
20. Moller JF, Nikolajsen L, Rodt SA, Ronning H, Carlsson PS. Thoracic paravertebral block for breast cancer surgery: a randomized double-blind study. Anesth Analg. 2007 Dec;105(6):1848-51, table of contents.
21. Pusch F, Freitag H, Weinstabl C, Obwegeser R, Huber E, Wildling E. Single-injection paravertebral block compared to general anaesthesia in breast surgery. Acta Anaesthesiol Scand. 1999 Aug;43(7):770-4.
22. Aufforth R, Jain J, Morreale J, Baumgarten R, Falk J, Wesen C. Paravertebral blocks in breast cancer surgery: is there a difference in postoperative pain, nausea, and vomiting? Ann Surg Oncol. 2012 Feb;19(2):548-52. Epub 2011 Jul 16.
23. Kitowski NJ, Landercasper J, Gundrum JD, De Maiffe BM, Chestnut DH, Bottcher ML, Johnson JM, Johnson RL. Local and paravertebral block anesthesia for outpatient elective breast cancer surgery. Arch Surg. 2010 Jun;145(6):592-4.
24. Coopey SB, Specht MC, Warren L, Smith BL, Winograd JM, Fleischmann K. Use of Preoperative Paravertebral Block Decreases Length of Stay in Patients Undergoing Mastectomy Plus Immediate Reconstruction. Ann Surg Oncol 2012; DOI 10.1245/s10434-012-2678-7. Epub ahead of print
25. Pu LL. The use of a pain pump for optimal postoperative pain management. Plast Reconstr Surg 2006;117:2066-9.
26. Naja MZ, Lonnqvist PA. Somatic paravertebral nerve blockade: incidence of failed block and complications. Anaesthesia. 2001; 56: 1184-8.
27. O'Brien, P.C. and Fleming. T.R. (1979). "A Multiple Testing Procedure for Clinical Trials." Biometrics, 35: 549-556.
28. Lan K. and DeMets D.L. (1983). "Discrete sequential boundaries for clinical trials." Biometrika, 70: 659-663.

APPENDICES

A Patient Pain Assessment Questionnaire
B Subjective Pain Survey
C BREAST-Q© (Pre-Operative)
D BREAST-Q© (Post-Operative)
E RAND-36 Questionnaire
F Quick DASH Questionnaire

Appendix A: Patient Pain Assessment Questionnaire

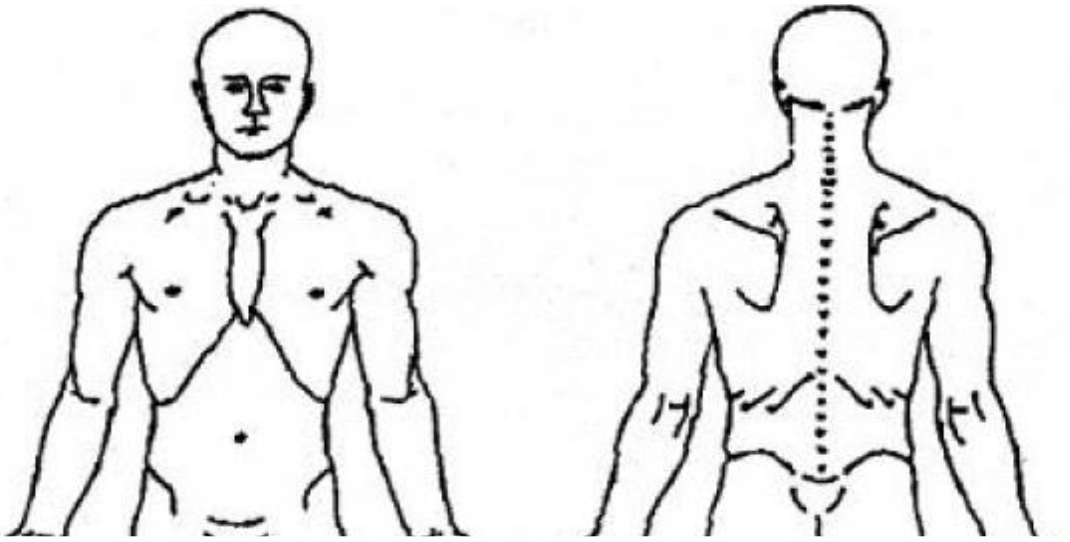
Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

Thank you for participating in this study. Please answer the following questions.

1. On the diagram, please place an X on the area(s) that hurt the most.



Right **Left** **Left** **Right**

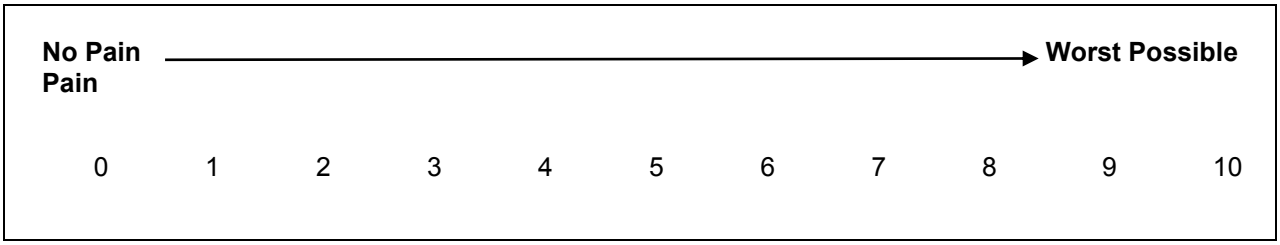
FRONT **BACK**

2. Please rate your pain by filling in on the scale below the number that best describes your pain at its worst in the last 24 hours.

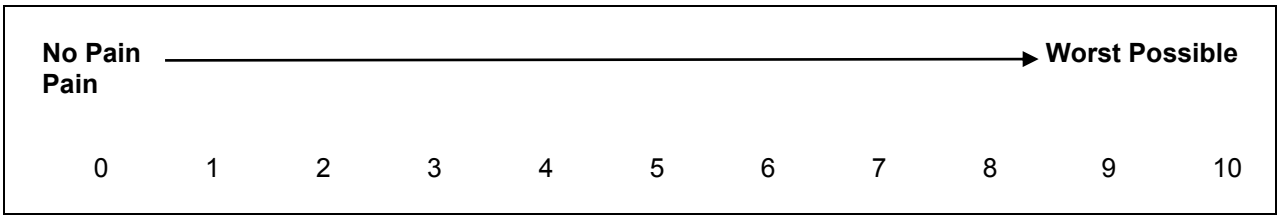
No Pain → **Worst Possible Pain**

0 1 2 3 4 5 6 7 8 9 10

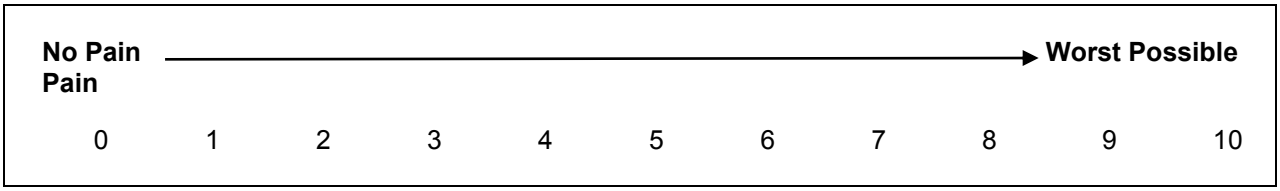
3. Please rate your pain by filling in on the scale below the number that best describes your pain at its least in the last 24 hours.



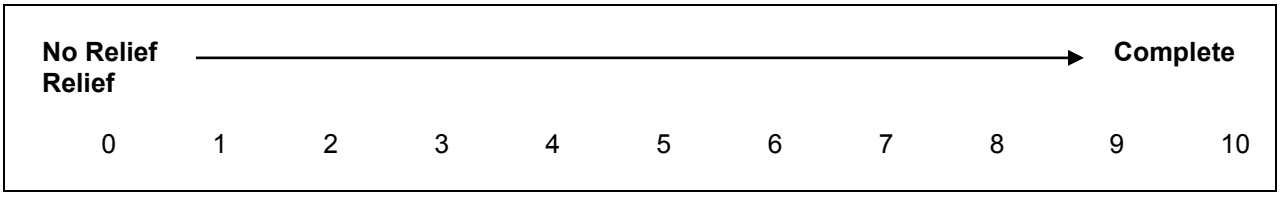
4. Please rate your pain by filling in on the scale below the number that best describes your pain on the <u>average</u> in the last 24 hours.



5. Please rate your pain by filling in on the scale below the number that best describes your pain <u>right now</u>.



6. In the past 24 hours, how much relief have pain treatments or medications provided? Please darken the circle that most shows how much relief you have received.



7. In the past 24 hours, how many times did you experience nausea?

None	One	Two	Three	Four	Five	Six	Seven	Eight	Nine +
0	1	2	3	4	5	6	7	8	9

8. In the past 24 hours, how many times did you experience vomiting?

None	One	Two	Three	Four	Five	Six	Seven	Eight	Nine +
0	1	2	3	4	5	6	7	8	9

Please darken the number in the box that best describes the extent your pain has interfered with your daily activities. If you are unsure how to answer a question, choose the answer that comes closest to how you feel.

9. Static Pain

Interference	No Interference → Complete										
a. Lying in Bed	0	1	2	3	4	5	6	7	8	9	10
b. Sitting up in Bed	0	1	2	3	4	5	6	7	8	9	10
c. Laughing	0	1	2	3	4	5	6	7	8	9	10
d. Coughing	0	1	2	3	4	5	6	7	8	9	10
e. Sneezing	0	1	2	3	4	5	6	7	8	9	10
f. Talking	0	1	2	3	4	5	6	7	8	9	10
g. Singing	0	1	2	3	4	5	6	7	8	9	10
h. Watching TV	0	1	2	3	4	5	6	7	8	9	10

10. Moving Pain

Interference	No Interference → Complete										
a. Getting out of Bed	0	1	2	3	4	5	6	7	8	9	10
b. Bending	0	1	2	3	4	5	6	7	8	9	10
c. Bathing Yourself	0	1	2	3	4	5	6	7	8	9	10
d. Dressing Yourself	0	1	2	3	4	5	6	7	8	9	10
e. Lifting	0	1	2	3	4	5	6	7	8	9	10
f. Carrying Groceries	0	1	2	3	4	5	6	7	8	9	10
g. Climbing Stairs	0	1	2	3	4	5	6	7	8	9	10
h. Stretching	0	1	2	3	4	5	6	7	8	9	10

11. Please darken one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

Does not interfere → Completely
Interferes

0 1 2 3 4 5 6 7 8 9 10

B. Mood

Does not interfere → Completely
Interferes

0 1 2 3 4 5 6 7 8 9 10

C. Relations with other people

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

D. Sleep

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

E. Enjoyment of Life

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

F. Ability to Concentrate

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

G. Appetite

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

H. Overall Quality of Life

Does not interfere → **Completely**
Interferes

0 1 2 3 4 5 6 7 8 9 10

Appendix B: Subjective Pain Survey

Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

Thank you for participating in this study. After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

On a scale of 1 to 5, please indicate how painful you believe these scenarios are:

	Not painful at all	A little painful	Somewhat painful	Quite painful	Extremely painful
a. Biting one's tongue?	1	2	3	4	5
b. An average toothache?	1	2	3	4	5
c. Burning one's hand on a stove?	1	2	3	4	5
d. Badly spraining one's ankle?	1	2	3	4	5
e. Average migraine headache?	1	2	3	4	5
f. Receiving an intramuscular injection?	1	2	3	4	5
g. Stubbing one's toe really hard?	1	2	3	4	5
h. The initial pain from a bee sting?	1	2	3	4	5

Appendix C: BREAST-Q© Reconstruction Module

Preoperative Questionnaire

Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, or if you have had a mastectomy, with your breast area in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	How comfortably your bras fit?	1	2	3	4
c.	Being able to wear clothing that is more fitted?	1	2	3	4
d.	How you look in the mirror unclothed?	1	2	3	4

2. With your breasts in mind, or if you have had a mastectomy, with your breast area in mind, in the past 2 weeks, how often have you felt:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Confident in a social setting?	1	2	3	4	5
b.	Emotionally able to do the things that you want to do?	1	2	3	4	5
c.	Emotionally healthy?	1	2	3	4	5
d.	Of equal worth to other women?	1	2	3	4	5
e.	Self-confident?	1	2	3	4	5
f.	Feminine in your clothes?	1	2	3	4	5
g.	Accepting of your body?	1	2	3	4	5
h.	Normal?	1	2	3	4	5
i.	Like other women?	1	2	3	4	5
j.	Attractive?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

3. In the past 2 weeks, <u>how often</u> have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Neck pain?	1	2	3	4	5
b.	Upper back pain?	1	2	3	4	5
c.	Shoulder pain?	1	2	3	4	5
d.	Arm pain?	1	2	3	4	5
e.	Rib pain?	1	2	3	4	5
f.	Pain in the muscles of your chest?	1	2	3	4	5
g.	Difficulty lifting or moving your arms?	1	2	3	4	5
h.	Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i.	Tightness in your breast area?	1	2	3	4	5
j.	Pulling in your breast area?	1	2	3	4	5
k.	Nagging feeling in your breast area?	1	2	3	4	5
l.	Tenderness in your breast area?	1	2	3	4	5
m.	Sharp pains in your breast area?	1	2	3	4	5
n.	Shooting pains in your breast area?	1	2	3	4	5
o.	Aching feeling in your breast area?	1	2	3	4	5
p.	Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (PRE OPERATIVE)

4. In the past 2 weeks, with your abdomen (tummy area) in mind, how often have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Difficulty sitting up because of abdominal muscle weakness (e.g. getting out of bed)?	1	2	3	4	5
b.	Difficulty doing everyday activities because of abdominal muscle weakness (e.g. making your bed)?	1	2	3	4	5
c.	Abdominal discomfort?	1	2	3	4	5
d.	Abdominal bloating?	1	2	3	4	5
e.	Lower back pain?	1	2	3	4	5

5. In the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How your abdomen looks?	1	2	3	4

6. Thinking of your sexuality, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a.	Sexually attractive in your clothes?	1	2	3	4	5	N/A
b.	Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c.	Confident sexually?	1	2	3	4	5	N/A
d.	Satisfied with your sex-life?	1	2	3	4	5	N/A
e.	Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f.	Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions

BREAST-Q© RECONSTRUCTION MODULE (PRE OPERATIVE)

Appendix D: BREAST-Q© Reconstruction Module

Postoperative Questionnaire

Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

The following questions are about your breasts and breast reconstruction surgery. After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
e.	How you look in the mirror clothed?	1	2	3	4
f.	The shape of your reconstructed breast(s) when you are wearing a bra?	1	2	3	4
g.	How normal you feel in your clothes?	1	2	3	4
h.	The size of your reconstructed breast(s)?	1	2	3	4
i.	Being able to wear clothing that is more fitted?	1	2	3	4
j.	How your breasts are lined up in relation to each other?	1	2	3	4
k.	How comfortably your bras fit?	1	2	3	4
l.	The softness of your reconstructed breast(s)?	1	2	3	4
m.	How equal in size your breasts are to each other?	1	2	3	4
n.	How natural your reconstructed breast(s) looks?	1	2	3	4
o.	How naturally your reconstructed breast(s) sits/hangs?	1	2	3	4
p.	How your reconstructed breast(s) feels to touch?	1	2	3	4
q.	How much your reconstructed breast(s) feels like a natural part of your body?	1	2	3	4
r.	How closely matched your breasts are to each other?	1	2	3	4
s.	How your reconstructed breast(s) look now compared to before you had any breast surgery?	1	2	3	4
t.	How you look in the mirror unclothed?	1	2	3	4

This question is about breast reconstruction using IMPLANTS. If you do not have an implant(s) please skip to question 3. If you do have an implant(s), please answer question 2 below.

2. In the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	The amount of rippling (wrinkling) of your implant(s) that you can see?	1	2	3	4
b.	The amount of rippling (wrinkling) of your implant(s) that you can feel?	1	2	3	4

3. These questions ask how you feel about the outcome of your breast reconstruction surgery. Please indicate how much you agree or disagree with each statement:

		Disagree	Somewhat Agree	Definitely Agree
a.	Having reconstruction is much better than the alternative of having no breast(s).	1	2	3
b.	I would encourage other women in my situation to have breast reconstruction surgery.	1	2	3
c.	I would do it again.	1	2	3
d.	I have no regrets about having the surgery.	1	2	3
e.	Having this surgery changed my life for the better.	1	2	3
f.	The outcome perfectly matched my expectations.	1	2	3
g.	It turned out exactly as I had planned.	1	2	3

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

4. With your breasts in mind, in the past 2 weeks, how often have you felt:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Confident in a social setting?	1	2	3	4	5
b.	Emotionally able to do the things that you want to do?	1	2	3	4	5
c.	Emotionally healthy?	1	2	3	4	5
d.	Of equal worth to other women?	1	2	3	4	5
e.	Self-confident?	1	2	3	4	5
f.	Feminine in your clothes?	1	2	3	4	5
g.	Accepting of your body?	1	2	3	4	5
h.	Normal?	1	2	3	4	5
i.	Like other women?	1	2	3	4	5
j.	Attractive?	1	2	3	4	5

5. Thinking of your sexuality, since your breast reconstruction, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a.	Sexually attractive in your clothes?	1	2	3	4	5	N/A
b.	Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c.	Confident sexually?	1	2	3	4	5	N/A
d.	Satisfied with your sex-life?	1	2	3	4	5	N/A
e.	Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f.	Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

6. In the past 2 weeks, <u>how often</u> have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Neck pain?	1	2	3	4	5
b.	Upper back pain?	1	2	3	4	5
c.	Shoulder pain?	1	2	3	4	5
d.	Arm pain?	1	2	3	4	5
e.	Rib pain?	1	2	3	4	5
f.	Pain in the muscles of your chest?	1	2	3	4	5
g.	Difficulty lifting or moving your arms?	1	2	3	4	5
h.	Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i.	Tightness in your breast area?	1	2	3	4	5
j.	Pulling in your breast area?	1	2	3	4	5
k.	Nagging feeling in your breast area?	1	2	3	4	5
l.	Tenderness in your breast area?	1	2	3	4	5
m.	Sharp pains in your breast area?	1	2	3	4	5
n.	Shooting pains in your breast area?	1	2	3	4	5
o.	Aching feeling in your breast area?	1	2	3	4	5
p.	Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

The following questions are about reconstruction using a TRAM or DIEP flap (i.e., reconstruction using skin and fat from your abdomen/tummy area). If you do not have a TRAM or DIEP flap, please skip to question 10. If you do have a TRAM or DIEP flap, please answer the following questions:

7. In the past 2 weeks, with your abdomen (tummy area) in mind, how often have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Difficulty sitting up because of abdominal muscle weakness (e.g. getting out of bed)?	1	2	3	4	5
b.	Difficulty doing everyday activities because of abdominal muscle weakness (e.g. making your bed)?	1	2	3	4	5
c.	Abdominal discomfort?	1	2	3	4	5
d.	Abdominal bloating?	1	2	3	4	5
e.	Abdominal bulging?	1	2	3	4	5
f.	Tightness in your abdomen?	1	2	3	4	5
g.	Pulling in your abdomen?	1	2	3	4	5
h.	Lower back pain?	1	2	3	4	5

8. In the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How your abdomen looks?	1	2	3	4
b.	The position of your navel (belly button)?	1	2	3	4
c.	How your abdominal scars look?	1	2	3	4

9. In the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How your abdomen feels now compared to before your surgery?	1	2	3	4
b.	How your abdomen looks now compared to before your surgery?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

This question is about NIPPLE reconstruction. If you did <u>not</u> have nipple reconstruction, please skip to question 11. If you did have nipple reconstruction, please answer question 10 below.

10. In the past 2 weeks, how <u>satisfied or dissatisfied</u> are you with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The shape of your reconstructed nipple(s)?	1	2	3	4
b. How your reconstructed nipple(s) and areola(s) look?	1	2	3	4
c. How natural your reconstructed nipple(s) look?	1	2	3	4
d. The color of your reconstructed nipple/areolar complex?	1	2	3	4
e. The height (projection) of your reconstructed nipple(s)?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

11. How satisfied or dissatisfied were you with the information you received from your plastic surgeon about:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How the breast reconstruction surgery was to be done?	1	2	3	4
b.	Healing and recovery time?	1	2	3	4
c.	Possible complications?	1	2	3	4
d.	The options you were given regarding types of breast reconstruction?	1	2	3	4
e.	The options you were given regarding timing of your breast reconstruction (i.e. same time as your mastectomy versus later)?	1	2	3	4
f.	The pros and cons of the timing of your breast reconstruction?	1	2	3	4
g.	How long the process of breast reconstruction would take from start to finish?	1	2	3	4
h.	What size you could expect your breasts to be after reconstructive surgery?	1	2	3	4
i.	How much pain to expect during recovery?	1	2	3	4
j.	What you could expect your breasts to look like after surgery?	1	2	3	4
k.	How long after reconstruction surgery it would take to feel like yourself/feel normal again?	1	2	3	4
l.	How the surgery could affect future breast cancer screening (e.g. mammogram, self examinations)?	1	2	3	4
m.	Lack of sensation in your reconstructed breast(s) and nipple(s)?	1	2	3	4
n.	What other women experience with their breast reconstruction surgery?	1	2	3	4
o.	What the scars would look like?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

12. These questions ask about your <u>plastic surgeon</u>. Do you feel that he/she:

		Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a.	Was competent?	1	2	3	4
b.	Gave you confidence?	1	2	3	4
c.	Involved you in the decision-making process?	1	2	3	4
d.	Was reassuring?	1	2	3	4
e.	Answered all your questions?	1	2	3	4
f.	Made you feel comfortable?	1	2	3	4
g.	Was thorough?	1	2	3	4
h.	Was easy to talk to?	1	2	3	4
i.	Understood what you wanted?	1	2	3	4
j.	Was sensitive?	1	2	3	4
k.	Made time for your concerns?	1	2	3	4
l.	Was available when you had concerns?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

13. These questions ask about <u>members of the medical team other than the surgeon</u> (e.g. nurses and other doctors who looked after you in the hospital when you had your breast reconstruction surgery). Did you feel that they:

		Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a.	Were professional?	1	2	3	4
b.	Treated you with respect?	1	2	3	4
c.	Were knowledgeable?	1	2	3	4
d.	Were friendly and kind?	1	2	3	4
e.	Made you feel comfortable?	1	2	3	4
f.	Were thorough?	1	2	3	4
g.	Made time for your concerns?	1	2	3	4

14. These questions ask about <u>members of the office staff</u> (e.g. secretaries and office nurses). Did you feel that they:

		Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a.	Were professional?	1	2	3	4
b.	Treated you with respect?	1	2	3	4
c.	Were knowledgeable?	1	2	3	4
d.	Were friendly and kind?	1	2	3	4
e.	Made you feel comfortable?	1	2	3	4
f.	Were thorough?	1	2	3	4
g.	Made time for your concerns?	1	2	3	4

Please check that you have answered all the questions

BREAST-Q© RECONSTRUCTION MODULE (POST OPERATIVE)

Appendix E: RAND-36 Item Short Form Survey

Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

1. **In general, would you say your health is:**

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

The following items are about activities your might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** flights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

21. How much bodily pain have you had during the past 4 weeks?

None	Very Mild	Mild	Moderate	Severe	Very Severe
1	2	3	4	5	6

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks . . .

	All of the Time	Most of the Time	A Good Bit of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5
24. Have you been a very nervous person?	1	2	3	4	5
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
26. Have you felt calm and peaceful?	1	2	3	4	5
27. Did you have a lot of energy?	1	2	3	4	5
28. Have you felt downhearted and blue?	1	2	3	4	5
29. Did you feel worn out?	1	2	3	4	5
30. Have you been a happy person?	1	2	3	4	5
31. Did you feel tired?	1	2	3	4	5

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people.	1	2	3	4	5
34. I am as healthy as anybody I know.	1	2	3	4	5
35. I expect my health to get worse.	1	2	3	4	5
36. My health is excellent.	1	2	3	4	5

Thank you for participating in this survey.
Please make sure you have answered all of the questions.

Appendix F: Quick DASH Questionnaire

Subject Number: _____ Study Personnel: _____

Last Name: _____First Name: _____

MRN: _____ DOB: _____ Date: ___/___/_____ Time: _____

*Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\left[\frac{\text{sum of n responses}}{n}\right] - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may <u>not</u> be calculated if there is greater than 1 missing item.