THE USE OF LIPOSOMAL BUPIVACAINE FOR PAIN CONTROL FOLLOWING MASTECTOMY AND IMMEDIATE IMPLANT BASED BREAST RECONSTRUCTION

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CCCWFU # 99517

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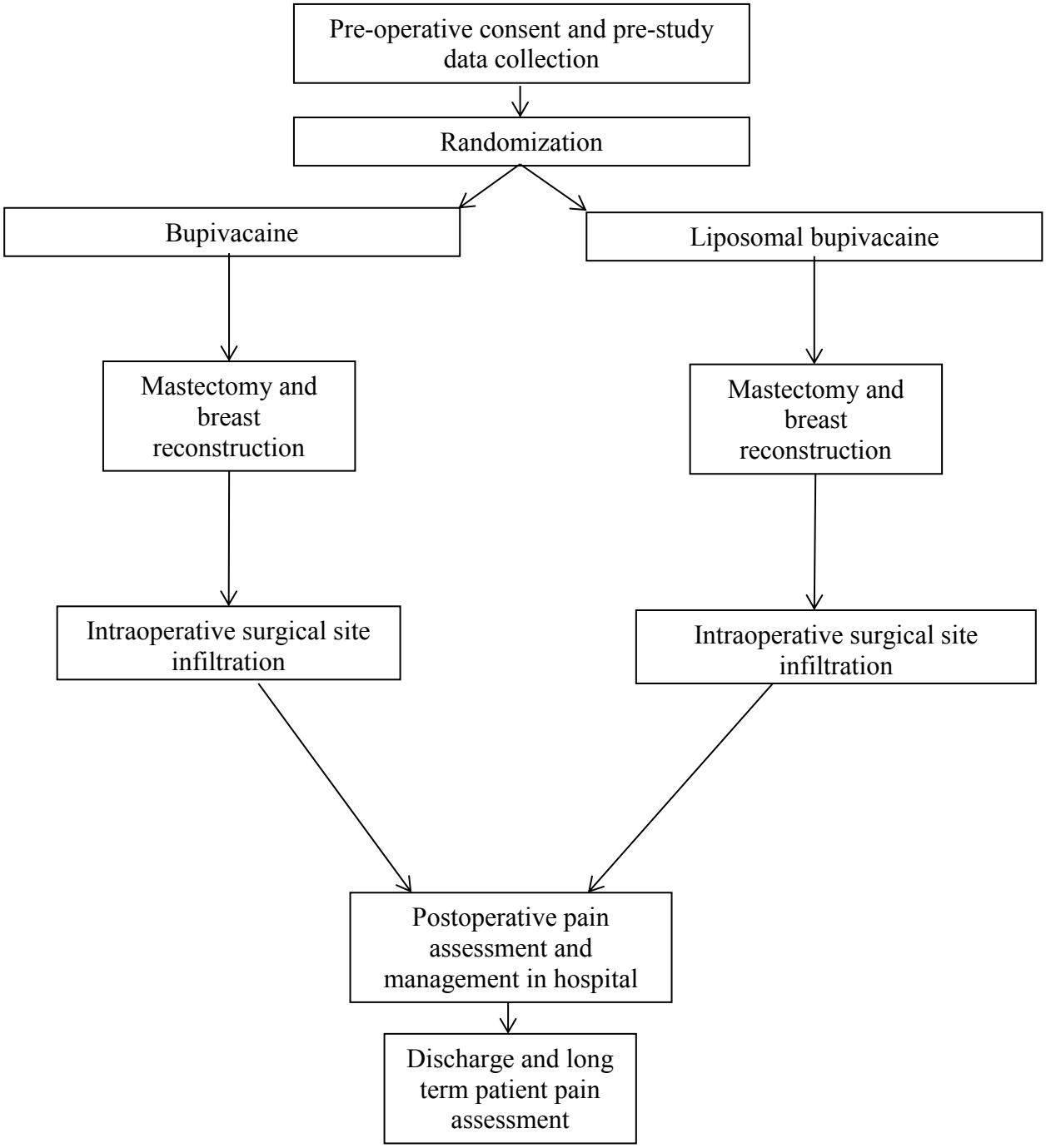
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1.0 Introduction and Background

Breast reconstruction defines the final step for many women on a long road to recovery from breast cancer. Reconstruction of the breast mound following mastectomy has several benefits in psychosocial functioning, body image and satisfaction with breast appearance, and sexual well-being[1-4]. However, reconstruction at the same time as mastectomy has been linked to higher post-operative pain[5]. As in any surgical procedure, post-operative pain control has a major impact on patient satisfaction and important outcome measures such as length of stay, readmission rates, and overall hospital costs[6-8]. In particular, poor post-operative pain control in the cancer population has a negative impact on physical functioning, with decreased ability to perform activities of daily living, social functioning, with decreased interest in hobbies and contact with friends, and can increase feelings of anxiety and depression[9]. In fact, fear of post-surgical pain has been shown to be a major reason that women refuse breast reconstruction surgery[10].

Implant based breast reconstruction is a widely used and well accepted technique with 86,013 procedures performed in the United States in 2015 vs 20,325 flap based breast reconstruction procedures[11]. However, this technique has disadvantages in relation to post-operative pain. Compared to autologous breast reconstruction, implant based techniques have been linked to higher requirements of post-operative benzodiazepines, nonsteroidal anti-inflammatory drugs, and narcotics as well as higher pain scores in the immediate post-operative period and one year after surgery[5,12]. Tissue expander based techniques in particular lead to even higher narcotic use and morphine equivalents than single staged implant reconstruction[5].

In an effort to decrease pain control, it is common practice for local anesthetics to be infiltrated into the surgical wound. Individual studies have shown that infiltrations with bupivacaine specifically have decreased intraoperative and postoperative narcotic use, decreased pain scores in the immediate postoperative period [24-26]. However, upon meta-analysis of randomized clinical trials studying the effect of wound infiltration with bupivacaine or ropivacaine it was found that postoperative pain severity was only decreased at 2 hours postoperatively and postoperative analgesic consumption did not change[27]. In light of this, there continues to be a need for improvement in postoperative pain management for mastectomy and subsequent breast reconstruction.

One such medication which has been suggested for improvement in pain control after mastectomy and breast reconstruction is Exparel (Pacira Pharmaceuticals, Inc., San Diego, CA). It is a relatively recent bupivacaine multi-vesicular liposomal delivery system that allows slow release of bupivacaine, resulting in local anesthetic effects for up to 72-96 hours after injection. It is a safe pain control modality with a similar side effects profile to bupivacaine HCL and does not compromise breast implant integrity[13-14].

Side effects of Exparel primarily includes GI upset (nausea and vomiting) which can occur in greater than 10% of patients. More rare side effects include hypotension (2-10%), insomnia (2-10%), pruritus (3%), postoperative anemia (2-10%), and muscle spasm (2-10%). Similar to other local anesthetics, dose related toxicity can occur and can lead to central nervous system excitation or depression. Exparel has a half-life of 24-34 hours and is hepatically metabolized and renally excreted. It should be used in caution with patients with moderate-severe hepatic or renal impairment because of the increased risk of toxicity. Exparel may increase the toxicity of lidocaine and bupivacaine. Bupivacaine can be administered with or immediately before Exparel as long as the milligram dose ratio of bupivacaine to Exparel is not greater than 1:2. Furthermore, Exparel may increase the effect of neuromuscular blocking agents. Exparel is not recommended in pregnant patients as there have been no studies conducted in this population and high doses used in animal models have been shown to decrease fetal

survival. It has been FDA approved for administration into the surgical site and the recommended a standard dosing for breast surgery of 266 mg (20 ml)[28].

Multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials have been performed for Exparel use in postoperative pain control for bunionectomy and hemorrhoidectomy. In the bunionectomy trial, it was found that with injection of Exparel there was a statistically significant reduction of cumulative pain levels over the first 24 hours after surgery[29]. Similarly, in the hemorrhoidectomy trial, it was found that the Exparel group had a decreased cumulative pain score at 72 hours[30].

Furthermore, liposomal bupivacaine has been shown to improve outcome measures including mean hospital stay and post-operative pain scores in a wide range of procedures from abdominal wall reconstruction to thoracotomies and sternotomies[15,16]. In retrospective studies, the use of Exparel decreased immediate postoperative pain associated with breast reconstruction compared with IV and oral narcotics and bupivacaine pain pumps. It also showed a significant decrease in mean length of stay compared to IV and oral narcotic pain management[18]. Up to this point, there have been no prospective studies examining the effects of Exparel on outcome measures when used in tissue expander based breast reconstruction. We believe that its use will decrease post-operative pain and will lead to improved performance in outcome measures.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 The primary objective of this clinical study is to evaluate the effect of Exparel on mean postoperative pain levels in patients who have undergone mastectomy and breast reconstruction within the first 48 hours. We hypothesize that Exparel will decrease mean postoperative pain levels within the first 48 hours.

2.2 Secondary Objective(s)

2.2.1 To evaluate the effect of liposomal bupivacaine on cumulative pain control within the first 48 hours after mastectomy and breast reconstruction
2.2.2 To evaluate the effect of liposomal bupivacaine on the amount of postoperative narcotic use after mastectomy and breast reconstruction for the first month after surgery
2.2.3 To evaluate the effect of liposomal bupivacaine on length of hospital stay after mastectomy and breast reconstruction
2.2.4 To evaluate the effect of liposomal bupivacaine on hospital readmission rates a within 2 months after mastectomy and breast reconstruction
2.2.5 To evaluate the effect of liposomal bupivacaine on the occurrence of opioid adverse effects within the first week of surgery after mastectomy and breast reconstruction
2.2.6 To evaluate the effect of liposomal bupivacaine on the trajectory of postoperative pain control within 2 months after mastectomy and breast reconstruction

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 All patients who receive a bilateral mastectomy with only immediate sub-pectoral implant based breast reconstruction
3.1.2 Age ≥ 18 years
3.1.3 Ability to understand and the willingness to sign an IRB-approved informed consent document.
3.1.4 Patients who receive tissue expander placement or direct permanent implant placement will be included in the study.
3.1.5 ASA patient status I-III patients

3.2 Exclusion Criteria

3.2.1 Patients who receive an autologous tissue reconstruction.
3.2.2 Patients who receive a unilateral reconstruction.
3.2.3 Patients who are expected to undergo axillary lymph node dissection
3.2.4 Patients who have undergone breast irradiation
3.2.5 Patients who abuse narcotics or have chronic pain (using greater than 40 mg equivalents of oxycodone per day)
3.2.6 Patients who are wards of the state
3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bupivacaine or liposomal bupivacaine.
3.2.8 Pregnant women are excluded from this study because pregnancy precluded immediate breast reconstruction in our patient population.
3.2.9 Patients who weigh less than 50 kg, as there can be dose related toxicities of the bupivacaine dosing used in this study
3.2.10 Patients with moderate-severe hepatic or renal impairment because of the increased risk of toxicity.
3.2.11 Patients receiving bilateral mastectomy with immediate pre-pectoral implant based breast reconstruction

3.3 Inclusion of Women and Minorities

Women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

We expect approximately 5% of study participants to be Hispanic/Latino (N=5). We plan to enroll at least 10% Black or African American (N=10), 1% American Indian/Alaska Native (N=1), 5% Asian (N=5). Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered in WISER prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient: All patients will be registered in WISER

1.

To complete the registration process, the study team will:

- assign a patient study number
- notify the pharmacy via faxed physician order form
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome of this study is the mean visual analog scores (scale of 0-10) within the first 48 hours postoperatively. This will be measured every 12 hours for the first 48 hours and will be assessed by the level of breast pain associated with arm movements while eating.

5.1.1.1 Visual analog scores in mastectomy patients with oral and IV narcotics are approximately 5.0 at 24 hours and 4.8 at 48 hours[17]

5.1.1.2 For patients with local infiltration of Liposomal bupivacaine after implant based reconstruction, visual analog scores at 24hrs were 3.8 on average[18]

5.2 Secondary Outcomes

5.2.1 Area under the curve visual analog scores (scale 0-10) during the first 48 hours postoperatively.

5.2.1.1 For patients undergoing submuscular augmentation mammoplasty, the area under the curve for pain scores at 72 hours for liposomal bupivacaine infiltration is 441 +/- 182 and for bupivacaine infiltration is 461 +/- 181[20]

5.2.2 Morphine equivalents used within the first month postoperatively

5.2.2.1 The number of doses of oral narcotics (hydrocodone-acetaminophen 1 tablet) for patients with immediate tissue expander reconstruction without other measure of pain control has been 4.2 at 24 hours and 4.0 at 48 hours[17]. This is approximately 3.3 morphine equivalents

5.2.2.2 We would expect the patients treated with liposomal bupivacaine to use an average of 2.5 intravenous morphine equivalents at the 48-hour point and decreased morphine equivalents in the liposomal bupivacaine over the first postoperative month.

5.2.3 Length of stay for hospitalization after mastectomy and breast reconstruction

5.2.3.1 Length of stay for patients undergoing mastectomy and immediate reconstruction has been shown to be 41-47 hours on average[21]

5.2.3.2 We believe liposomal bupivacaine will shorten this time to 36 hours±12 in the liposomal bupivacaine group, but not in the bupivacaine groups.

5.2.4 Readmission rates to the hospital within 2 months after mastectomy and breast reconstruction

5.2.4.1 Patients who underwent tissue expander breast reconstruction have a readmission rate of approximately 4.34%[22]. We anticipate a readmission rate of approximately 2% Patients will be informed that if they are expected to undergo an axillary lymph node dissection at the time of surgery then they will be excluded from the study. Patients who are undergoing sentinel lymph node biopsies will be included in the study, but if their nodes are positive and there is an intraoperative decision to pursue axillary lymph node dissection they will subsequently be excluded from the study.

5.2.5 Frequency of postoperative opioid related adverse effects within the first week of surgery. This includes nausea, vomiting, pruritus, allergy, respiratory depression.

5.2.5.1 After immediate breast reconstruction with implants, patients receiving bupivacaine had a 40% incidence of nausea and vomiting. Those not receiving a local anesthetic had a 75% incidence of nausea and vomiting[17]

5.2.5.2 We predict a 30% incidence of opioid related adverse events in our liposomal bupivacaine group

5.2.6 Trajectory of postoperative recovery from pain within the first 2 months

5.2.6.1 Growth curve analysis of pain intensity with movement scores over the first two months, using an initial log (time) model and a Bayesian change point analysis

5.2.6.2 Groups will be compared for intercept and slope of the trajectory of pain intensity up to the first change point

5.2.6.3 For the entire population, the impact of the optimism-catastrophizing continuum and other predictive factors for intercept and slope will be explored

6.0 Treatment Plan

	Preoperative Visit	Day of Surgery	Upon discharge home	1st 12hr post discharge	2nd 12hr post discharge	3rd 12hr post discharge	4th 12hr post discharge	1 week postop	3 weeks postop	5 weeks postop
Life Orientation Test-Revised	X									
PROMIS-Depression	X									
PROMIS-Anxiety	X									
Pain Catastrophizing Scale	X									
Baseline Pain Assessment	X									
Enrollment and informed consent	X									
Receive surgical site infiltration of Exparel or bupivacaine		X								
Q 12 hour pain scores				X	X	X	X			
Patent diary of narcotic use and pain rating			X					X		
Disability assessments								X	X	X
Pain assessments								X	X	X

6.1 Study-Related Activities

Patient involvement in the study will be initiated in the plastic surgery clinic. Eligible subjects will be identified prior to surgery. Potential subjects will be contacted either by phone or during their clinic visit, informed consent will be obtained and a 30-minute preoperative assessment will be performed. Patients will be informed that if they are expected to undergo an axillary lymph node dissection at the time of surgery then they will be excluded from the study. Patients who are undergoing sentinel lymph node biopsies will be included in the study, but if their nodes are positive and there is an intraoperative decision to pursue axillary lymph node dissection they will subsequently be excluded from the study. Also, we will record demographic and history information, including existing pain elsewhere, and administer questionnaire-based measures of psychological state, physical function, and baseline pain (Table 1, Appendix F). Questionnaire responses will be entered via the cancer center REDCap data entry form. From these questionnaires, we will place each participant on a dimensional continuum that describes their general cognitive style. We will use multidimensional scaling (MDS) to force catastrophizing and optimism as 2 ends of this continuum.

Table 1. Preoperative Questionnaires
Life Orientation Test-Revised (LOT-R)
PROMIS- Depression
PROMIS- Anxiety
Pain Catastrophizing Scale (PCS)

These two constructs describe cognitive styles that are strongly inversely associated with each other; MDS will provide the optimal weights to best order individuals on this latent scale. Studies have examined the interplay of these constructs with other psychological concepts such as acceptance, pain-related disability and psychosocial adjustment and have found that both are reliably associated with the positive and negative aspects of the adjustment to pain.

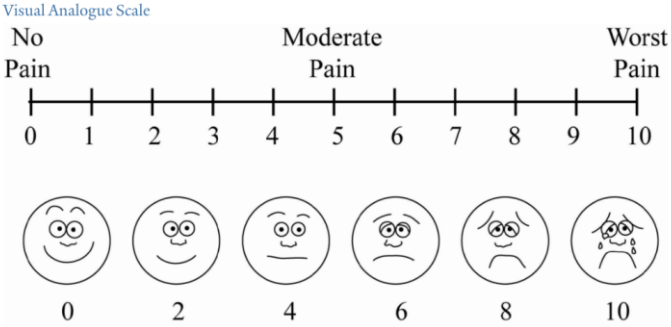
The research coordinator will then assign the patients a study number. On the day of surgery, each patient will be randomized to be in one of the following two groups for perioperative local anesthetic infiltration:

1. Local infiltration of bupivacaine
2. Local infiltration of liposomal bupivacaine

The study will be double blinded to both patients and providers including plastic and general surgeons involved in their operative care. We will enroll our patients in pharmacy randomization program, in which the pharmacy will deliver the appropriate medication per assigned group.

To monitor our primary outcomes, patients will be asked to rate their pain level on a visual analog scale (Table 2, Appendix Z) with activity every 12-hours after surgery during their post-procedure stay. The activity for which they will rate their pain will be the arm movements associated with eating. In the hospital, their visual analog scores will be provided to each patient in person by their nurse every 12 hours. Subject's pain scores will continue to be recorded every 12 hours via a phone call from a study team member for the first 48 hours after discharge. Additionally, while in the hospital, the amount of narcotics used will be recorded and converted into morphine equivalents.

Table 2: Visual Analog Scale



Upon discharge, patients will be given a sheet to record their pain level and the amount of narcotics & benzodiazepines used (Appendix K). Both the amount of narcotics & benzodiazepines and the pain level are to be reported at the time of taking any narcotics & benzodiazepines. Patients will follow up with our clinic at 1 week, 3 weeks, and 5 weeks postoperatively. At week 1 patients will bring in their medication and pain diary, and fill out a pain assessment (Appendix G) in addition to a questionnaire assessing breast cancer surgery

disability (Appendix H)[23]. During subsequent appointments made at 3 and 5 weeks postoperatively, they will be assessed and receive the pain assessment and breast cancer surgery disability assessments as well. When tissue expansion is initiated will be determined by the primary surgeon, but we will track the dates of the initiation of expansion as this will impact pain scores within the electronic medical record.

Secondary outcomes including length of hospital stay, adverse opioid effects and re-admission rate will be tracked by their electronic medical record. Upon reviewing the questionnaires, if a subject is determined to have high levels of depression, our team will make them aware of the resources available in the psychiatry department and a contact number will be provided to them.

6.2 Treatment Administration

Patients assigned to the local infiltration with bupivacaine group will receive a total 60 ml of 0.25% bupivacaine with 30 ml delivered to each breast. Patients assigned to the local infiltration of liposomal bupivacaine will receive a total of 20 ml liposomal bupivacaine (266 mg) with 10 ml of 0.25% bupivacaine and 30 ml of 0.9% sodium chloride. These injections will occur at the end of the mastectomy and prior to the insertion of the tissue expander implant. The local anesthetic will be injected into the chest wall and skin flaps. Attending physicians and resident physicians will receive prior instruction regarding correct placement of the local anesthetic so that it will be consistently placed in the same locations with similar volume distribution. After this intraoperative injection, patients will not receive any more doses of local anesthetics.

6.3 General Concomitant Medication and Supportive Care Guidelines

This local anesthetic will get delivered at the time of surgery in an opaque syringe. Standardized anesthetic criteria will be applied to all patients enrolled in the study. Pre-operatively, all patients will receive multi-modal therapy, such as acetaminophen, celecoxib, and gabapentin or pregabalin unless contraindicated. Intraoperatively, patients will only receive short acting fentanyl for analgesia. Intraoperative ketamine and dexamethasone will be avoided. A notification will populate in EPIC once the patient is linked to the study in WISER to notify the anesthesia provider. Postoperative non-opioid medications will supplement as needed opioid mediations for analgesic management.

Patients will receive full supportive care as medically necessary, including transfusions of blood and blood products, antibiotics, antiemetics, etc. Medications considered necessary for the patient's well-being may be given as long as they are considered safe in the postoperative period and clinically indicated. The reason(s) for treatment, dosage, and dates of treatment will be recorded on the flow sheets.

6.4 Duration of Follow Up

Patients will be seen at one week, three weeks and five weeks postoperatively at which time they will receive pain and disability assessments.

7.0 Adverse Events List and Reporting Requirements

7.1 Adverse Event List for Liposomal Bupivacaine:

Common adverse reactions (incidence 2-10%): pyrexia, dizziness, peripheral edema, anemia, hypotension, pruritis, tachycardia, headache, insomnia, anemia postoperative, muscle smasm, hemorrhagic anemic, back pain, somnolence, procedural pain. [28]

Rare adverse reactions (incidence <2%): chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.[28]

None of these adverse effects are expected to occur as a result of the administration of liposomal bupivacaine.

7.2 Adverse Event List for Bupivacaine:

The major cause of adverse reactions is secondary to high plasma levels of the medication. In this setting, CNS reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, drowsiness, unconsciousness. High doses can depress the myocardium leading to decreased cardiac output, heart block, hypotension, bradycardia, arrhythmias, cardiac arrest. Allergic reactions are rare but can include urticarial, pruritus, erythema, angioneurotic edema, tachycardia, nausea, vomiting, anaphylactoid-like symtpoms[31].

None of these adverse effects are expected to occur as a result of the administration of liposomal bupivacaine.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

7.4 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE. All adverse events will be recorded and the data will be managed in WISER. As such, the STRC will have access to all adverse events in the course of the study.

7.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

8.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the commercial agents administered in this study can be found in Section 7.1 and 7.2.

8.1 Pharmaceutical Accountability

Drug accountability logs will be maintained for all agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

8.2 Liposomal Bupivacaine

Product description: 20 ml liposomal bupivacaine (266 mg)

Solution preparation: Will be diluted in 10 ml of 0.25% Bupivacaine and 30 ml of 0.9% NaCl for a total solution volume of 60 ml per patient (30 ml per breast)

Storage requirements: Vials of Exparel should be inverted multiple times to re-suspend the particles immediately prior to withdraw from the vial.

Stability: Diluted suspensions should be used within 4 hours of the preparation.

Route of administration: Injection into surgical site including mastectomy skin flaps and wound bed after mastectomy and before breast reconstruction.

Disposal: There should be no additional product to dispose after injection

8.3 Bupivacaine

Product description: 60 ml of 0.25% bupivacaine

Solution preparation: No further dilution is required. 30 ml of 0.25% bupivacaine will be delivered to each breast.

Storage requirements: Can be stored at room temperature. The pharmacy will store and create the syringes including the medications to be administered.

Stability: The dosage of the above bupivacaine is stable and will not change over time

Route of administration: Injection into surgical site including mastectomy skin flaps and wound bed after mastectomy and before breast reconstruction.

Disposal: There should be no additional product to dispose after injection

9.0 Data Management

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Life Orientation Test-Revised	REDCap
PROMIS- Depression	REDCap
PROMIS- Anxiety	REDCap
Pain Catastrophizing Scale	REDCap
Visual analog scores	REDCap
Daily Pain Diary and Pain Rating	REDCap
Weekly Disability Assessment	REDCap
Adverse Effects	WISER

10.0 Statistical Considerations

10.1 Analysis of Primary Objective

10.1.1 The study will allow for an attrition rate of 10%. Assuming a similar standard deviation in pain score at 48 hours for the local infiltration of liposomal bupivacaine and bupivacaine arms, with a 2-sided alpha of 0.05 and power of 80%, the study would have the ability to detect an effect size (absolute value of difference in sample means divided by the standard deviation) of 0.6 between the 2 groups with 25 subjects per arm. We will recruit 25 subjects per arm; if there is no attrition, with the same alpha and power as above, the study would have the ability to detect an effect size of 0.57. The primary outcome will be the pain score observed at 48 hours. To test for differences in these scores between the 2 arms, an independent t-test will be used; if the observed p-value is <0.05, statistical significance will be assumed. Two-sided ANOVA will be performed for statistical analysis once data collection is complete.

10.2 Analysis of Secondary Objective

10.2.1 For the area under the curve of pain scores at 48 hours, prior studies have found that the area under the curve for pain scores at 72 hours for liposomal bupivacaine infiltration is 441 +/- 182 and for bupivacaine infiltration is 461 +/- 181[20]. A sample size of 40 in each group will have 80% power to detect a difference in means of approximately 25% (115 units) between a Bupivacaine mean, m_1, of 461 and a Liposomal Bupivacaine mean, m_2, of 346 assuming that the common standard deviation is 181 using a two group t-test with a 0.05 two-sided significance level. Our study will be powered to detect this difference; we will use an independent t-test to assess statistical significance.

10.2.2 For postoperative narcotic use, prior studies have found the average use of morphine equivalents at 48 hours after mastectomy and tissue expander placement is 3.3[17]. This study will also have the ability to detect an effect size of 0.6 between groups, with 45 per group, a two-sided alpha of 0.05, and 80% power. We would expect the patients treated with liposomal bupivacaine to be have a lower average use. We will use an independent t-test to test for differences between groups; if the data are not normally distributed, a log transformation will be used prior to using the t-test.

10.2.3 For length of stay, the reported LOS has been shown to be 41-47 hours on average [21]. We believe Exparel will shorten this time; the study will have the ability to detect an effect size of 0.60 between the 2 groups. We will use an independent t-test to test for differences between groups; if the data are not normally distributed, a log transformation will be used prior to using the t-test.

10.2.4 For readmission rates, patients who underwent tissue expander breast reconstruction have a readmission rate of approximately 4.34%[22]. We anticipate a readmission rate of approximately 2%. Our study is not powered to detect differences in the 2 arms in this parameter.

10.2.5 For opioid related adverse effects, we predict a 50% incidence of opioid related adverse events in our study. With 45 per group, our study is not powered to detect differences between the 2 arms unless the difference is much larger than anticipated. With a 60%

rate, 2-sided alpha of 0.05 and 80% power, we could detect a difference of 31% between the 2 arms using a Fisher's Exact Test

10.2.6 For trajectory of postoperative recovery from pain, Growth curve analysis of pain intensity with movement scores over the first two months, using an initial log (time) model and a Bayesian change point analysis

10.2.6.1 Groups will be compared for intercept and slope of the trajectory of pain intensity up to the first change point

10.2.6.2 For the entire population, the impact of the optimism-catastrophizing continuum and other predictive factors for intercept and slope will be explored

10.3 Power and Sample Size

We will have a power of 80%, as described in 10.1.1, with a sample size of 25 patients in each arm for a total of 50 patients

10.4 Accrual Rate

We plan on accruing 25 new patients per year until the goal of 50 total patients is reached.

10.5 Estimated Study Length

Estimated study length will be approximately 2 years. This will include patient enrollment through the 5 week patient follow up period.

10.6 Interim Analysis Plan

We will plan on performing an interim analysis for the primary outcome and secondary outcomes after there are at least 10 patients in each treatment group in order to detect the evidence of severe side effects in either group. We will perform a secondary analysis after there are at least 20 patients in each group to monitor for more rare side effects including but not limited to bradycardia, tachycardia, respiratory distress, hypotension or neurological depression.

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The following Appendices are required for all WFBCCC cancer treatment protocols.

Add additional appendices as needed.

***ALL** data collection forms must be included as protocol appendices at the time the protocol is submitted to the WFBCCC Protocol Review Committee (PRC) for review.*

Appendix A – Eligibility Checklist

IRB Protocol No. ___ ___ ___ ___ ___ ___ ___ ___	**WFBCCC Protocol No.___ ___ ___ ___ ___**
Study Title: THE USE OF LIPOSOMAL BUPIVACAINE FOR PAIN CONTROL FOLLOWING MASTECTOMY AND BREAST RECONSTRUCTION	
Principal Investigator: Christopher Runyan, M.D., Ph.D.	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
All patients who receive a bilateral mastectomy with immediate implant based breast reconstruction	☐	☐	
Age >18 years	☐	☐	
Ability to understand and willingness to sign IRB-approved informed consent document	☐	☐	
Patients who will receive a tissue expander or a direct permeant implant for breast reconstruction	☐	☐	
ASA patient status I-III	☐	☐	
Patients having sub-pectoral implant placement			
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Patients who receive an autologous tissue reconstruction	☐	☐	
Patients who receive a unilateral reconstruction	☐	☐	
Patients who weigh < 50 kg	☐	☐	
Patients who will undergo axillary lymph node dissection	☐	☐	
Patients who abuse narcotics or have chronic pain (using greater than 40 mg equivalents of oxycodone per day)	☐	☐	
Patients who are wards of the state	☐	☐	
History of allergic reactions attributed to compounds of similar chemical or biologic composition to bupivacaine or liposomal bupivacaine.	☐	☐	
Patients having pre-pectoral implant placement			

Pregnant women are excluded from this study because liposomal bupivacaine is a/an class C agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with liposomal bupivacaine, breastfeeding should be discontinued if the mother is treated with liposomal bupivacaine.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: "Pathology report, 01/01/14" or "Clinic note, 01/01/14"

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D – Mandatory STRC SAE Reporting Guidelines

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 8/17/2016**

Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on WFBCCC Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **WFBCCC Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at WFBCCC. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for WFBCCC Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a WFBCCC Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.

What is considered an SAE under this mandatory procedure?

Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study

treatment or if they occur within 30 days of last study treatment (even if patient begins a new treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		**Grade 4**		**Grade 5**	
	Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

can be used to identify events. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2
and Phase 3 Interventional Trials

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.
   This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements to complete the electronic STRC form:
Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#
4. WFBCCC(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician
    i. Is This Event Related to Protocol Treatment?

ii. Is Suspension of the Protocol Needed?
iii. Any Changes to Consent or Protocol Needed?
iv. Was Nature or Severity of Event Unexpected?

15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma”,”)
22. Your Name
23. Your Email
24. Confirm Your Email

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, WFBCCC; Chair, PRC; Section Head, Hematology/Oncology. 6-7970 / 6-2701 / Pager 336-806-9308
Antonius Miller, MD – Hematology Oncology 6-7970 / 6-7414 / Pager 704-637-8384
Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397
Kathryn Greven, MD – Vice Chair – Radiation Oncology. 3-3600 / 3-6505 / Pager 336-806-8314
Marissa Howard-McNatt, MD – General Surgery 6-0545 / 336-806-6438
Mercedes Porosnicu, MD- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right

to agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.
Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Acronyms and Definitions

STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
IRB-Institutional Review Board
WFBCCC-Comprehensive Cancer Center Wake Forest University
ORIS-Oncology Research Information System
NCI-National Cancer Institute
CPDM-Clinical Protocol and Data Management
Interventional Trials-Therapeutic Level 1 and Level 2 trials
Therapeutic Level 1-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.
Therapeutic Level 2-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or prevent cancer.

Appendix E – Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: _____ **PID:** _____ **MRN:** _____

Cycle Start Date: _____ **Cycle End Date:** _____ **Cycle #:** _____

Adverse Event CTC Term	**Value** (-5 if non-numeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	***Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxicity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** 1=IRB 2=STRC 3=FDA 4=Sponsor

*Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix F – Pre-Operative Questionnaires

Revised Life Orientation Test (LOT-R)

Instructions:
Please answer the following questions about yourself by indicating the extent of your agreement using the following scale:

|0| = strongly disagree
|1| = disagree
|2| = neutral
|3| = agree
|4| = strongly agree

Be as honest as you can throughout, and try not to let your responses to one question influence your response to other questions. There are no right or wrong answers.

_____ 1. In uncertain times, I usually expect the best
_____ 2. It's easy for me to relax
_____ 3. If something can go wrong for me, it will
_____ 4. I'm always optimistic about my future
_____ 5. I enjoy my friends a lot
_____ 6. It's important for me to keep busy
_____ 7. I hardly ever expect things to go my way
_____ 8. I don't get upset too easily
_____ 9. I rarely count on good things happening to me
_____ 10. Overall, I expect more good things to happen to me than bad

Scoring:
1. Reverse code items 3, 7, and 9 prior to scoring (0=4) (1=3) (2=2) (3=1) (4=0).
2. Sum items 1, 3, 4, 7, 9, and 10 to obtain an overall score.

Note: Items 2, 5, 6, and 8 are filler items only. They are not scored as part of the revised scale.

The revised scale was constructed in order to eliminate two items from the original scale, which dealt more with coping style than with positive expectations for future outcomes. The correlation between the revised scale and the original scale is .95.

Reference:
Scheier, M. F., Carver, C. S., and Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A re-evaluation of the Life Orientation Test. *Journal of Personality and Social Psychology*, 67, 1063-1078.

PROMIS Item Bank v. 1.0 – Emotional Distress – Depression - Short Form 8b

Emotional Distress - Depression -- Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days....

	Never	Rarely	Sometimes	Often	Always
I felt worthless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt that I had nothing to look forward to.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt helpless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like a failure.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt depressed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt unhappy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt hopeless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Emotional Distress – Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Instructions: Please reflect on past painful experiences and indicate the degree to which you experienced each of these thoughts and feelings when experiencing pain. The circle the appropriate number based on the scale below:

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

cats

Appendix G – Pain Assessment
Subject Number:___ ___ ___ ___ ___ ___ ___ ___ DATE: __ __/__ __/__ __TIME: __ __:__ __AM/PM

1 - Rate the intensity of your worst pain in the past 24 hours related to your operated breast/chest.

0 1 2 3 4 5 6 7 8 9 10

2 – Please rate the intensity of breast pain that you have while eating.

0 1 2 3 4 5 6 7 8 9 10 Cannot Do

3 – If it has been one month or longer since your surgery please complete the following question:

Please lift your arms to the sides of your body at a 90-degree angle. Rate the intensity of breast pain that you have during this activity.

0 1 2 3 4 5 6 7 8 9 10 Cannot Do

Not Applicable

4 - Rate your level of disability in the past 24 hours to do normal daily activities.

0 1 2 3 4 5 6 7 8 9 10

5 - Rate your level of disability in the past 24 hours to do activities you enjoy.

0 1 2 3 4 5 6 7 8 9 10

6 - Did you take prescription pain pills in the past 24 hours? YES NO

If yes please circle the medication below and complete question 5b

6a1 – Oxycodone

6a2 - Hydromorphone (Dilaudid)

6a3 - Hydrocodone + acetaminophen (Vicodin, Norco)

6a4 Valium

6b - In the last 24 hours, how many prescription pills have you taken for your pain?

_____

Appendix H - Disability Assessment

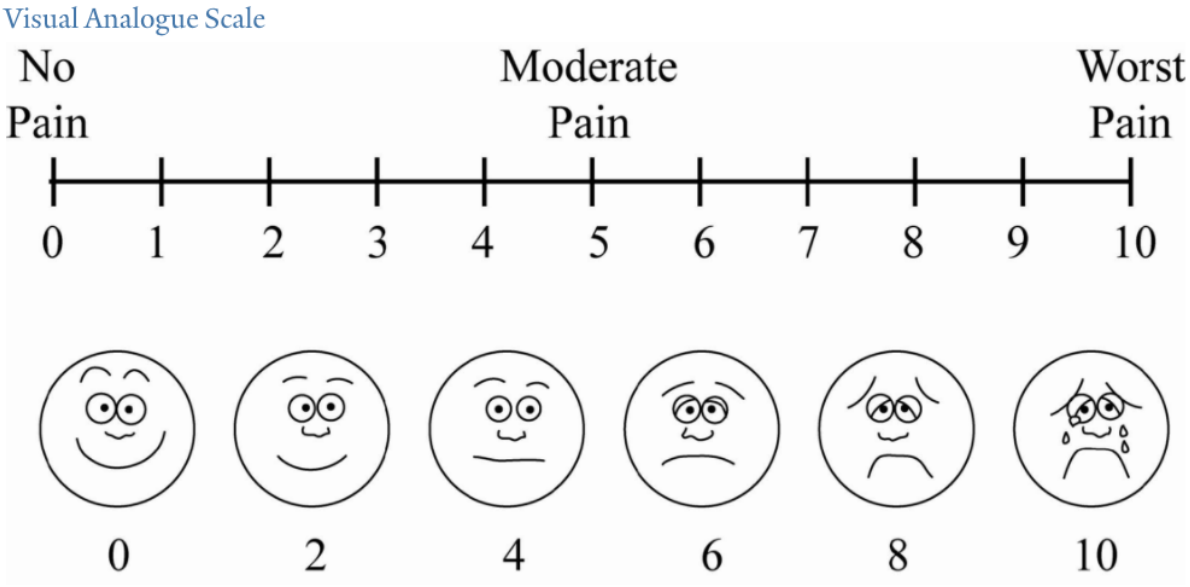
For the following, indicate whether pain since your surgery has affected your ability to perform these activities:

Subject Number:___ ___ ___ ___ ___ ___ ___ ___ DATE: __ __/__ __/__ __ TIME: __ __:__ __AM/PM

6a: Carry or lift children	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6b: Carrying grocery bags, luggage, or heavy bags	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6c: Do Laundry	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6d: Kitchen chores, cooking	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6e: Opening a heavy door	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6f: Put on a brassiere	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6g: Put on a coat	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6h: Reaching high shelves, over your head	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6i: Sleep	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**

6j: Take a sweater on or off	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6k: Vacuuming or washing floors	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**
6l: Washing hair / neck	**1 - Not relevant, I don't do this** **2 - I can do this without any problem** **3 - I can do this but with difficulties due to pain** **4 - I can't do his due to pain from my surgery**

Appendix I- Visual Analog Scale



Appendix J – Off-Study Form

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Christopher Runyan, M.D. Date: __ __/__ __/__ __

Name of Person Competing form_____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject withdrawn from the study? Yes ☐ No ☐

Reason(s) for withdrawal:

1. ☐ Patient exhibited progression of disease

2. ☐ Unacceptable toxicity

   If Yes, Please specify whether the toxicity was:
   ☐ From Bupivacaine
   ☐ From Liposomal Buvipucaine
   ☐ From BOTH

☐ Other _____

3. ☐ Patient withdraw

   If Yes, Please specify what portion of the study the subject wishes to withdraw from:

   ☐ For just the Drug A administration only
   ☐ For just the Drug B administration only
   ☐ For both
   ☐ For all components of the research study (including follow up in the medical record)

4. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)

5. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)

6. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)

7. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)

8. ☐ Termination of the clinical trial by the clinical sponsor

Comment:

If reason for withdrawal includes #4, 5, 6, or 7 then please add comments clarifying this information)_____

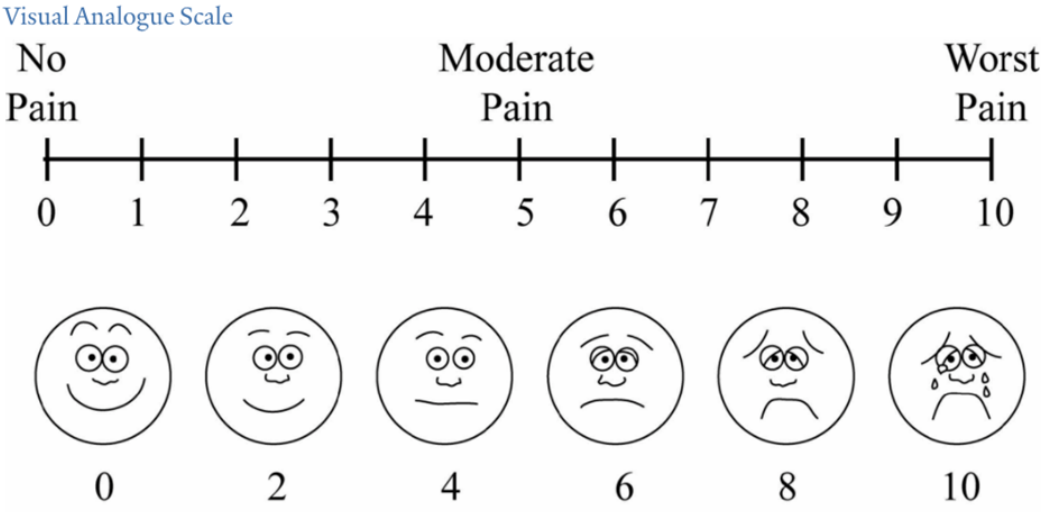
_____

_____

_____

Appendix K- Pain Medication Diary. Assists patients in recording the amount and time of narcotic and benzodiazepine use.

Please use the scale below for reference when providing Pain Rating:



	Date	**Pain Medication Used (Include dose)**	**Number of pills taken**	**Time**	**Pain Rating (*see scale above for reference*)**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					

16					
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