TITLE: A Phase III Study of Pre-operative Transversus Abdominis Plane Blocks using the Nimbus Ambulatory Infusion System in Patients Undergoing Abdominal Free Flap-based Breast Reconstruction

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Reasons for Changes: Edits for typos, clarify study timeline, update document storage location

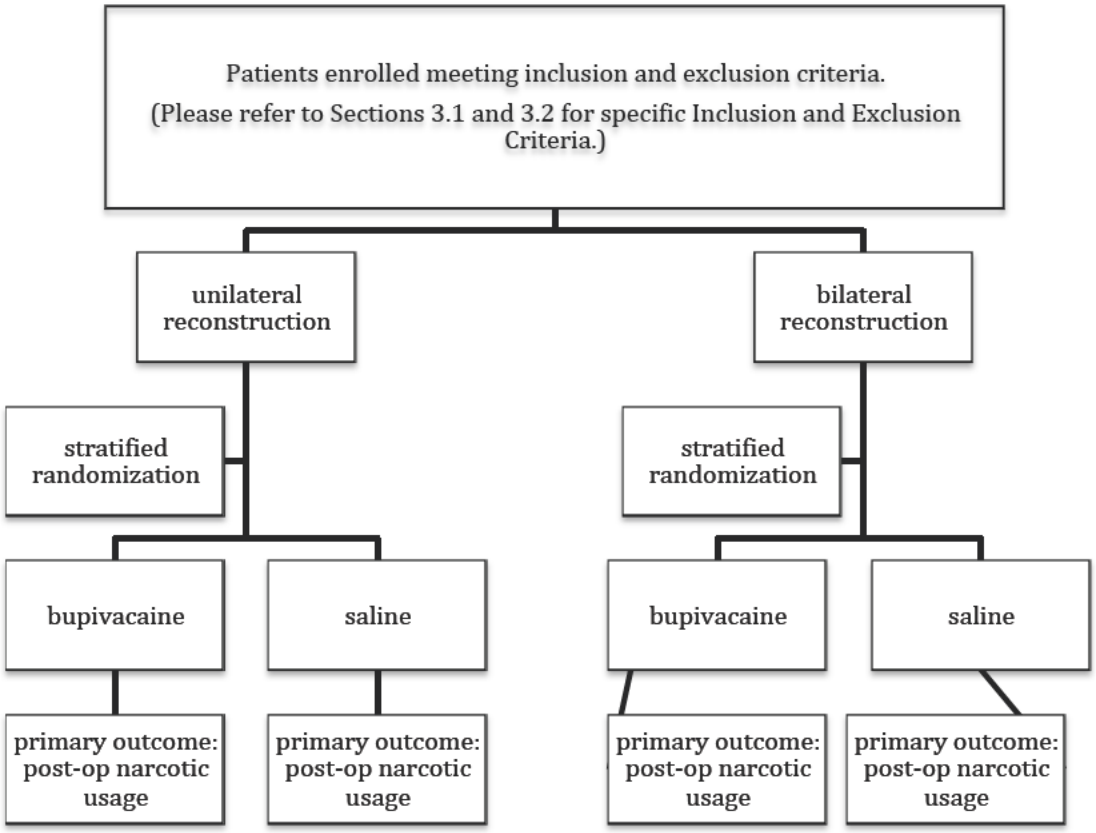
TABLE OF CONTENTS

PROTOCOL SYNOPSIS

In the table below summarize the basic aspects of this research. This is to be used as a quick reference guide. Remove any section that is not relevant to the research.

TITLE	A Randomized Double-blinded, Placebo-Controlled Trial: Use of Transversus Abdominis Plane (TAP) Block in Breast Cancer Patients Undergoing Microsurgical Breast Reconstruction with Abdominal Free Flap
STUDY PHASE	Phase III
INVESTIGATIONAL PRODUCT OR PROCEDURE	Pre-operative Transversus Abdominis Plane Block with Nimbus Ambulatory Infusion System
PRIMARY OBJECTIVE(S)	Post-operative narcotic usage
SECONDARY OBJECTIVE(S)	i. Post-operative pain scores ii. Post-operative anti-emetic usage iii. Time to ambulation iv. Time to first bowel movement v. Patient-perceived quality of life
TREATMENT SUMMARY	Two study arms: • Intervention: infusion of 0.125% bupivacaine through TAP catheter • Control: infusion of saline through TAP catheter
SAMPLE SIZE	128

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Include additional abbreviations as needed. Remove any unnecessary abbreviations.

AE	Adverse event
CRF	Case report form
IRB	Institutional Review Board
IV	Intravenous
MG	Milligrams
ML	Milliliter
OME	Oral morphine equivalent
PCA	Patient-controlled analgesia
PD	Protocol director
PO	Per os
POD	Post-op day
Q4H	Every 4 hours
RCT	Randomized controlled trial
SAE	Serious adverse event
TAP	Transversus abdominis plane
VAS	Visual analog scale
VTBI	Volume to be infused

1. OBJECTIVES

1.1. Primary Objective

The primary objective is to determine if pre-operative transversus abdominis plane (TAP) blocks with continued infusion of local anesthetic post-operatively affect post-operative narcotic usage as compared to a placebo TAP block.

1.2. Secondary Objectives

1.2.1 To determine if pre-operative TAP blocks with continued infusion of local anesthetic post-operatively affect post-operative pain scores as compared to a placebo TAP block.

1.2.2 To determine if pre-operative TAP blocks with continued infusion of local anesthetic post-operatively affect anti-emetic usage as compared to a placebo TAP block.

1.2.3 To determine if pre-operative TAP blocks with continued infusion of local anesthetic post-operatively affect time to ambulation post-operatively as compared to a placebo TAP block.

1.2.4 To determine if pre-operative TAP blocks with continued infusion of local anesthetic post-operatively affect time to first bowel movement as compared to a placebo TAP block.

1.2.5 To determine if pre-operative TAP blocks with continued infusion of local anesthetic post-operatively affect patient-reported quality of life as compared to a placebo TAP block.

2. BACKGROUND

2.1 Study Disease

Patient enrolled in our study with have a known or presumed diagnosis of breast cancer or are pursuing prophylactic treatment for which they are undergoing post-mastectomy breast reconstruction with abdominal free flap.

2.2 Study Agent/Device/Procedure

2.2.1 Nimbus Ambulatory Infusion System:

Product Description:

- Adjustable volume to be infused (VTBI), variable basal rate and bolus delivery
- Single patient use.

The Nimbus Ambulatory Infusion System is capable of carrying:

- Time stamped infusion parameters
- Incidences of bolus requests vs. bolus delivered

2.2.2 Transversus abdominis plane (TAP) block

The transversus abdominis plane (TAP) block is a peripheral nerve block that targets nerve roots T6 to L1, which innervate the anterior abdominal wall. The block is placed by administering local anesthetic into the fascial plane between the internal oblique muscle and the transversus abdominis muscle.[1, 2] TAP blocks have previously been show to improve immediate post-operative patient comfort and reduce post-operative narcotic usage in a variety of other abdominal surgeries including abdominoplasty, laparotomy, and cesarean section.[3-7]

2.2.3 Bupivacaine (Bupivacaine Hydrochloride)

Bupivacaine hydrochloride is an amide-type local anesthetic metabolized primarily in the liver via conjugation with glucuronic acid. Peak levels of bupivacaine in the blood are reached in 30 to 45 minutes following peripheral nerve block injection, followed by a decline to insignificant levels during the next three to six hours. The half-life of Bupivacaine Hydrochloride in adults is 2.7 hours. When administered in recommended doses and concentrations, Bupivacaine Hydrochloride does not ordinarily produce irritation or tissue damage.[8]

For clinicaltrials.gov compliance
Both the Nimbus Ambulatory Infusion System and the local anesthetic bupivacaine have been FDA approved for use for analgesia in patient in the United States.

2.3 Rationale

There are many options for post-mastectomy breast reconstruction including implants, pedicled muscle flaps, and free muscle flaps. With the development of advanced microsurgical techniques, free abdominal muscle flaps have become a popular option for breast reconstruction.[9, 10] For these patients, the speed of recovery and hospital length of stay following surgery are largely determined by the abdominal flap donor site rather than the breast recipient and resection site.[9]

Successful post-operative analgesia has been reported to decrease the incidence of both cardiopulmonary complications, in-hospital mortality, and healthcare costs, and it may also contribute to lower odds of death after surgery.[11, 12] In addition, when examining factors leading to expedited discharge following abdominal-based breast reconstruction surgery, use of a multimodal pain regimen was found to be predictive of successful early discharge.[13] Though post-operative opioids can decrease pain scores, opioids can also lead to adverse side effects including sedation, nausea, vomiting, constipation, and respiratory depression.[14] Because patients undergoing abdominal flap-based breast reconstruction have had abdominal muscle tissue manipulation, postoperative vomiting can increases the risk of incisional hernias and other surgical complications.

An increasingly utilized option for post-surgical pain management is a pre-operative nerve block targeting anesthetic directly to the nerve roots innervating the surgical field. In the setting of abdominal flap-based breast reconstruction, a transversus abdominis plane (TAP) nerve block accomplishes this goal for the abdominal incision. Several studies have evaluated the TAP block in abdominal flap-based breast reconstruction. Hivelin et al. evaluated bilateral ultrasound-guided TAP block in patients undergoing unilateral deep inferior epigastric perforator (DIEP) flap reconstruction and found that patients reported lower pain scores post-operatively and demonstrated lower narcotic usage in the first 24 hours, but not in subsequent time periods out to

48 hours after surgery. However, in this study only a single injection of local anesthetic was given intra-operatively, and this injection was performed by a surgeon in the operating room, rather than by an anesthesiologist in the pre-operative waiting area. The duration of block placement varied between 18 and 24 minutes, increasing the overall length of time in the operating room. In addition, Hivelin et al. only followed patients to 48 hours after reconstruction.[15] Furthermore, Wheble et al. performed a retrospective review of intra-operatively placed TAP blocks and found patients receiving the block had a shorter hospital length of stay, lower overall morphine usage, and less post-operative nausea and vomiting. However, this was a retrospective study with a small number of patients in each group (12 in the TAP group, and 15 in the non-TAP group).[16]

In addition, Zhong et al. conducted a prospective cohort study with TAP block catheters placed intra-operatively under direct visualization of fascial planes, and the anesthetic infusions continued until post- operative day 3. Zhong et al. compared this group of patients to a retrospective cohort from the same institution and found that patient who received TAP blocks had significantly less opioid usage than those who did not.[17] The group conducted a subsequent randomized double-blinded controlled trial with TAP catheters placed under direct vision, this time administering either local anesthetic or saline for controls and found similar results.[18]

A limitation of both studies by Zhong et al. is that patients undergoing both unilateral and bilateral reconstruction were combined, as were patients undergoing immediate and delayed reconstruction. Given that patients are subjected to twice the surgical insult in bilateral versus unilateral reconstruction, combining these patients into one cohort for analysis of post-operative pain may confound the results attained. Similarly, in delayed reconstruction, a repeat surgical incision is made at the site of the breast, whereas in immediate reconstruction, the same incision at the breast is used for both mastectomy and reconstruction.

In our study design, patients undergoing unilateral and bilateral reconstruction will be separated for both randomization and statistical analysis. We aim to further elucidate if the specific type of surgery changes the efficacy of the pre-operative TAP nerve block.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

- State the primary purpose for the protocol:
  - **Supportive Care**: protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects or mitigate against a decline in the subject's health or function. In general, supportive care interventions are not intended to cure a disease.
- State the interventional model:
  - **Parallel**: one of two groups in parallel for duration of study.
- State the number of intervention arms:
  - **Two intervention arms.**
- State whether the study will be masked:
  - **Double Blind**: both parties unaware of intervention assignment
- State whether the study is randomized: **Yes.**

- State type of primary outcome or outcome that the protocol is designed to evaluate: **Efficacy**

2.5 Correlative Studies Background

There are no planned correlative studies.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Prior diagnosis or presumed diagnosis of breast cancer or undergoing prophylactic treatment.

3.1.2 Greater than 18 years old.

3.1.3 Female.

3.1.4 Undergoing microsurgical breast reconstruction with abdominal free flap.

3.1.5 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria.

3.2.1 True allergy to local anesthetics or opioids.

3.2.2 History of addiction to narcotics within the last 24 months

3.2.3 History of chronic pain on opioids within the last 24 months.

3.2.4 Specific mental health issues such as schizophrenia or bipolar disorder.

3.2.5 Patients who are pregnant.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

Patients will be randomized within their surgery subtype (unilateral or bilateral) by the Stanford

Pharmacy to receive TAP catheters infusing either bupivacaine or saline. Randomization will occur using a computer software program to be implemented by the Pharmacy. The anesthetist placing the block, the surgeon performing the surgery, the nurses caring for the patient while hospitalized, and the research coordinators collecting data will be blinded to the randomization status.

3.5 Study Timeline

Primary Completion:
The study will reach primary completion approximately 48 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion approximately 52 months from the time the study opens to accrual.

4. TREATMENT PLAN

4.1 Pre-operative clinic visit

4.1.1 All patients undergoing microsurgical breast reconstruction for breast cancer with abdominal free flap are screened for enrollment.

4.1.2 Patients meeting inclusion criteria and not meeting exclusion criteria are enrolled. (See Appendix A for further details on inclusion and exclusion criteria.)

4.1.3 Consent forms for study enrollment are signed.

4.1.4 BREAST-Q[19] questionnaire filled out.

4.2 Hospitalization for reconstructive surgery

4.2.1 TAP Catheter Placement and Dosing:

On the day of surgery, bilateral TAP catheters will be placed using ultrasound guidance by the anesthesiologist in the pre-operative staging area prior to entering the operating room. Patients in the experimental group will receive an infusion of 0.125% bupivacaine and patients in the control group will receive an infusion of saline. Both groups will receive the following dosing:

- Initial bolus of 15mL pre-operatively
- 10mL bolus q4h intraoperatively with an option of 1-2mL per hour basal rate
- 10mL bolus q4h post-operatively with an option of 1-2mL per hour basal rate

TAP catheters will be discontinued on post-operative day (POD) 2, and the time will be recorded.

4.2.2 Post-Operative Pain Medication Regimen:

All patients will be provided with a patient controlled analgesia (PCA) infusion post- operatively providing IV hydromorphone. The PCA will be discontinued on POD2. Other pain medications available immediately after leaving the operating room will include the following:

- Acetaminophen IV or PO around the clock, per physician preference
- IV hydromorphone (dilaudid) 0.5 mg every 4 hours as needed for breakthrough pain, with an option to titrate up dose or frequency, per physician preference
- PO oxycodone 5-10 mg every 3 hours as needed for pain, with an option to titrate up dose or frequency, per physician preference
- Any pre-operative medications may be continued

4.2.3 Post-Operative Anti-Emetic Medication Regimen:

All patients will have available IV ondansetron (zofran) 4 mg every 4 hours as needed for nausea. Patients unable to take ondansetron will be given metocloprmiade (reglan).

4.2.4 Post-Operative Measurements:

Patients will be asked to rate their pain level on the Visual Analog Scale (VAS) every 4 hours while hospitalized unless they are sleeping. The total dosage of IV hydromorphone administered (via both the PCA and the as needed medications for breakthrough pain) will be recorded in 8-hour periods (midnight to 8am, 8am to 4pm, 4pm to midnight). The use of other pain medications, as well as anti-emetic medications, will be recorded in the same 8-hour periods. Time to ambulation, time to first bowel movement after surgery, and time to discharge will be recorded.

4.2.5 Evaluation for Discharge:

Patients will be evaluated daily for meeting discharge criteria as per normal Institution guidelines that are standard of care for patients undergoing flap-based breast reconstruction. That is, discharge criteria for patients on this study are the same as Institutional discharge criteria.

4.3 Post-operative follow-up (1-6 months post-operatively)

4.3.1 The post-operative BREAST-Q questionnaire[19] will be administered at a clinic visit 1-6 months after surgery. If the study subject is unable to attend clinic in person during this time period, they will be asked to return the post-operative BREAST-Q questionnaire via email or fax. If the study subject does not return the post-operative BREAST-Q survey after 3 attempts by phone or email, the subject will be considered lost to follow-up and no futher attempts will be made to have the patient complete the questionnaire.

4.4 General Concomitant Medication and Supportive Care Guidelines

Please refer to Section 4.2 above for details on concomitant medications.

4.5 Criteria for Removal from Study

Patients will be removed from the study if the study proves harmful to patient's health, if there is recurrence of cancer during study enrollment, if the patient withdraws consent at any time, and/or if the study protocol director deems it necessary to remove the patient from the study for any reason.

4.6 Alternatives

Sterile surgical technique and precautions will be utilized for placement of each TAP catheter. Alternative treatments for patients will include all pain medications offered for post-operative pain (detailed in Section 4.2).

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

5.1.1 Nimbus Ambulatory Infusion System

Product Description:

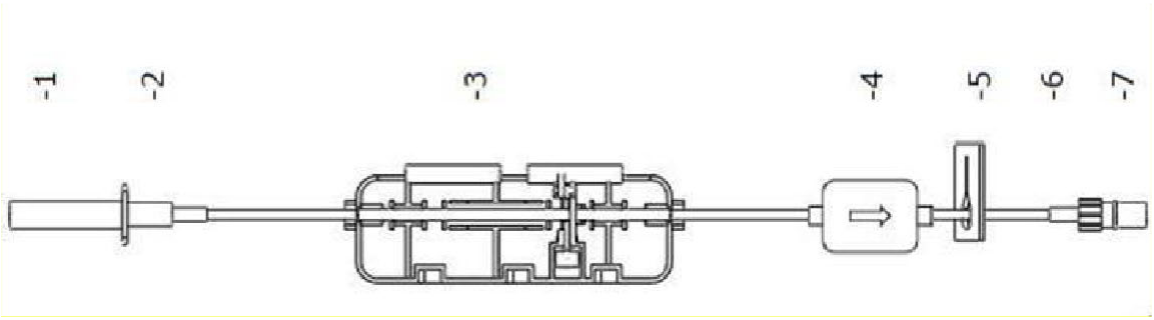
- Adjustable volume to be infused (VTBI), variable basal rate and bolus delivery

- Single patient use.
- Basal rate 0 – 14 mL/hr. Rate may be titrated during therapy delivery
- Optional keypad lockout function
- Kit comes with a pump, fanny pack, 10-day lithium ion battery, Clinician Guide and Patient Quick Reference Guide

Nimbus Infusion Pump IV Administration Set:

Product Description:

- 1 Each 67" (170cm) Long
- Priming Volume: 3mL (approx.)
- Fluid path is sterile, non-Pyrogenic
- One bag spike (1)
- One Cassette (3)
- One 1.2 Micron, air-eliminating Filter (4) One Slide Clamp (5)
- One Male Luer Lock Adaptor (6)



The Nimbus Ambulatory Infusion System is intended to deliver medications and/or fluids to a patient under the direction or supervision of a physician or other certified healthcare provider. The device is indicated for subcutaneous, epidural, perineural, and intravenous infusion.
For the purposes of the Implementation, the Nimbus Ambulatory Infusion System will be customized to the Institution protocol presently:

- Deliver a 15 mL bolus to establish the primary block
- Deliver a 10 mL auto-bolus every four hours intraoperatively, with the option for
- a 1 or 2 mL per hour basal rate
- Deliver a 10 mL per hour auto-bolus post-operatively, with the option for a 1 or 2 mL per hour basal rate

The Nimbus Ambulatory Infusion System is capable of carrying:

- Time stamped infusion parameters
- Incidences of bolus requests vs. bolus delivered

to provide Institution with access to infusion history data and patient interactions as a uniquely designed data carrier device.

The Nimbus Ambulatory Infusion System is intended to be used in an environment where patient care is provided by Healthcare Professionals, i.e. Physicians, Nurses, and Technicians, who will determine when use of the device is indicated, based upon their professional assessment of the

patient's medical condition.

5.1.2 Transversus abdominis plane (TAP) Nerve Block

The transversus abdominis plane (TAP) nerve block is a peripheral nerve block that targets nerve roots T6 to L1, which innervate the anterior abdominal wall. The block is placed by administering local anesthetic into the fascial plane between the internal oblique muscle and the transversus abdominis muscle.[1, 2] TAP nerve blocks have previously been show to improve immediate post-operative patient comfort and reduce post-operative narcotic usage in a variety of other abdominal surgeries including abdominoplasty, laparotomy, and cesarean section.[3-7]

5.1.3 Bupivacaine (Bupivacaine Hydrochloride)

As reported on FDA-approved drug products website:
<http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018053s055lbl.pdf>

"The onset of action with Bupivacaine Hydrochloride is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with Bupivacaine Hydrochloride than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced. After injection of Bupivacaine Hydrochloride for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. The half-life of Bupivacaine Hydrochloride in adults is 2.7 hours.

Amide-type local anesthetics such as Bupivacaine Hydrochloride are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of Bupivacaine Hydrochloride. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, Bupivacaine Hydrochloride does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

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

Bupivacaine Hydrochloride is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of Bupivacaine Hydrochloride solutions.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of Bupivacaine Hydrochloride up to 225 mg

with epinephrine 1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case. These doses may be repeated up to once every three hours. In clinical studies to date, total daily doses have been up to 400 mg."[8]

5.2 Availability

InfuTronix, LLC, will be providing the Nimbus Ambulatory Infusion System sets, at no cost to Stanford Hospital.

5.3 Agent Ordering

InfuTronix, LLC agrees to provide the Institution, at no cost to the Institution, as many as two hundred (200) units of the Product complete with appropriate patient accessories along with the relevant Documentation. In addition, in order to enable Institution to implement the Product, InfuTronix, LLC agrees to: (i) conduct a site survey of the Institution's facilities; (ii) provide the Product; and (iii) remove the Product upon the expiration of this Agreement. Risk of loss for Institution's existing equipment shall at all times remain with Institution. InfuTronix, LLC also agrees to provide training for Institution's medical staff and technical staff on how to properly use the Product, to provide technical support for device failures or problems, and to provide technical updates as required for both the hardware and software components of the Product.

InfuTronix, LLC Contact Information:
John LaFratta
Director of Sales and Business Development InfuTronix, LLC
[redacted]

5.4 Agent Accountability

The InfuTronix, LLC, Nimbus Ambulatory Infusion System products will be stored securely by the Department of Anesthesia. All stores of bupivacaine will be stored and dispensed by the Stanford Hospital Pharmacy, as is general protocol for all local anesthetics used for peri-operative analgesia.

6. DOSE MODIFICATIONS

Doses will be standardized across each patient group to the following, and no modifications shall be made:

- Initial bolus of 15mL pre-operatively
- 10mL bolus q4h intraoperatively with an option for 1-2mL per hour basal rate
- 10mL bolus q4h post-operatively with an option for 1-2mL per hour basal rate

The Intervention group will receive an infusion of 0.125% bupivacaine, while the Control/Placebo group will receive an infusion of normal saline.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

As reported on FDA-approved drug products website:
<http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018053s055lbl.pdf>

"The most commonly encountered acute adverse experiences which demand immediate counter measures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose related and due to high plasma levels which may result from over dosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Patients over 65 years, particularly those with hypertension, may be at increased risk for experiencing the hypotensive effects of Bupivacaine Hydrochloride. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance."[8]

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 after the last dose of the study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

There are no planned correlative studies.

9. STUDY CALENDAR

	Pre-Study	POD 0	POD 1	POD 2	POD 3-Discharge	1-6 months post-operatively
Investigational Treatment		X	X	X		
Informed consent	X					
Demographics	X					
Medical history	X					
Height	X					
Weight	X					
TAP catheter		X	X	X		
PCA		X	X	X		
Adverse event evaluation		X	X	X	X	
Evaluation for discharge[a]		X	X	X	X	
Pain evaluation	X	X	X	X	X	
BREAST-Q questionnaire	X					X

[a]Patients will be evaluated daily for meeting discharge criteria and discharged when all criteria are met (detailed in Section 4.2.5).

10. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

Primary Outcome Measure: Total oral morphine equivalents of narcotic used in first 48 hours post-operatively after breast reconstruction.

- **Title:** Post-operative Narcotic Usage
- **Time Frame**: First 48 hours post-operatively.
- **Safety Issue**: No

Note: Each outcome measure listed within the protocol will necessitate legally required results reporting to clinicaltrials.gov within one year after the completion of the primary outcome measure.

10.1 Primary Outcome Measure: Post-operative Narcotic Usage

10.1.1 Measurement Definition

Post-operative Narcotic Usage will be measured in total oral morphine equivalents (OME) calculated by summing all narcotics used in the first 48 hours post-operatively.

10.1.2 Measurement Methods

Post-operative Narcotic Usage will be measured by review the patient's chart and medication administration history and totaling all narcotics administered.

10.1.3 Measurement Time Points

Post-operative Narcotic Usage will be measured in 8-hour time intervals (midnights to 8am, 8am to 4pm, 4pm to midnight) while the patient is hospitalized. The primary outcome will evaluate total narcotic usage in the first 48 hours post-operatively.

10.2 Secondary Outcome Measure: Post-operative Pain Score

10.2.1 Measurement Definition

Post-operative Pain Score is defined using Visual Analog Scale (VAS), a patient reported pain score on a scale of 0-10**.**

10.2.2 Measurement Methods

Post-operative Pain Score will be measured by asking patient to rate their pain on the VAS.

10.2.3 Measurement Time Points

Post-operative Pain Score will be measured every 4 hours post-operatively unless the patient is sleeping.

10.3 Secondary Outcome Measure: Post-operative Anti-emetic Usage

10.3.1 Measurement Definition

Post-operative Anti-emetic Usage is defined as the total amount of IV ondansetron administered to a patient during the first 48 hours post-operatively.

10.3.2 Measurement Methods
Post-operative Anti-emetic Usage will be determined by examining the patient's chart and medication administration history.

10.3.3 Measurement Time Points
Post-operative Anti-emetic Usage will be examined during the first 48 hours post-operatively.

10.4 Secondary Outcome Measure: Time to Ambulation

10.4.1 Measurement Definition
Time to Ambulation is defined as the time to the first instance a patient is able to stand up and walk a few steps post-operatively.

10.4.2 Measurement Methods
The time of first ambulation will be recorded by the nurse on shift. Time to Ambulation will be calculated from midnight on POD 1.

10.5 Secondary Outcome Measure: Time to First Bowel Movement

10.5.1 Measurement Definition
Time to First Bowel Movement is defined as the time to the first instance a patient passes stool post-operatively.

10.5.2 Measurement Methods
The time of first bowel movement will be recorded by the nurse on shift. Time to First Bowel Movement will be calculated from midnight on POD 1.

10.6 Secondary Outcome Measure: Quality of Life

10.6.1 Measurement Definition
Quality of Life is defined as the calculated score from the BREAST-Q questionnaire.[19]

10.6.2 Measurement Methods
Quality of Life will be measured by having the patient fill out the BREAST-Q questionnaire pre-operatively, as well as post-operatively between 1-6 months after surgery.

10.6.3 Measurement Time Points
Quality of Life will be measured 1-6 months after surgery.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior

to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be maintained by Stanford Box account, a secure data storage platform, or in a locked office accessible only to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This study is a randomized double-blind, placebo-controlled clinical trial.

12.1.1 Randomization

Patients will be randomized within their group (unilateral or bilateral reconstruction) to receive either a true TAP catheter or a sham TAP catheter with saline infusion. The Stanford Pharmacy will randomize patients into the two groups.

12.2 Interim analyses

There are no planned interim analyses.

12.3 Descriptive Statistics and Exploratory Data Analysis

If applicable, describe plans for descriptive statistics and exploratory data analysis.

12.4 Primary Analysis

Post-operative Narcotic Usage

12.4.1 Analysis Population

Subjects will be grouped according to laterality of breast reconstruction (i.e., unilateral vs. bilateral). Within each group, experiment subjects will be compared to control subjects. A first

sensitivity analysis will explore the impact of missing data by replacing missing data with the more extreme values that favor the null hypothesis. A second sensitivity analysis will replace missing values with an extreme value that favors the alternative hypothesis. In both cases "extreme" is the largest or smallest value as applicable.

12.4.2. Analysis Plan
Differences between the two arms will be evaluated using an analysis of covariance model. The comparison of the two arms will be made adjusting for the variables used in the stratified randomization. The primary analysis will be a modified intent-to-treat principle (using recorded values where available regardless of compliance).

12.5 Secondary Analysis

12.5.1 Post-operative Pain Score

12.5.1.1 Analysis Population
Subjects will be grouped according to laterality of breast reconstruction (i.e., unilateral vs. bilateral). Within each group, experiment subjects will be compared to control subjects. Missing data will be dropped, and subjects who were non-adherent to the protocol will be excluded.

12.5.1.2 Analysis Plan
Data will be compared between the two groups using a two-tailed t-test.

12.5.2 Post-operative Anti-emetic Usage

12.5.2.1 Analysis Population
Subjects will be grouped by study intervention, with experimental subjects being compared to control subjects. Missing data will be dropped, and subjects who were non-adherent to the protocol will be excluded.

12.5.2.2 Analysis Plan
Differences between the two arms will be evaluated using an analysis of covariance model. The comparison of the two arms will be made adjusting for the variables used in the stratified randomization.

12.5.3 Time to Ambulation

12.5.3.1 Analysis Population
Subjects will be grouped by study intervention, with experimental subjects being compared to control subjects. Missing data will be dropped, and subjects who were non-adherent to the protocol will be excluded.

12.5.3.2 Analysis Plan
Time to ambulation will be evaluated using a Cox proportional hazards model. The comparison of the two arms will be made adjusting for the variables used in the stratified randomization.

12.5.4 Time to First Bowel Movement

12.5.4.1 Analysis Population

Subjects will be grouped by study intervention, with experimental subjects being compared to control subjects. Missing data will be dropped, and subjects who were non-adherent to the protocol will be excluded.

12.5.4.2 Analysis Plan

Time to first bowel movement will be evaluated using a Cox proportional hazards model. The comparison of the two arms will be made adjusting for the variables used in the stratified randomization.

12.5.5 Quality of Life

12.5.5.1 Analysis Population

Subjects will be grouped by study intervention, with experimental subjects being compared to control subjects. Missing data will be dropped, and subjects who were non-adherent to the protocol will be excluded.

12.5.5.2 Analysis Plan

Data will be compared between the two groups using a two-tailed t-test.

12.6 Sample Size

12.6.1 Accrual estimates

Based on data from prior years of patients undergoing post-mastectomy breast reconstruction, we estimate a total of 40 patients will be eligible for study enrollment each year. This number was determined by counting the number of patients who underwent eligible surgeries in 2014 at Stanford Hospital and Clinics. If study accrual falls short of what is expected, we will apply for IRB extension and continue study enrollment until the target sample size is reached. Our target sample size is 64 patients in each the experimental and control groups for a total of 128 patients.

12.6.2 Sample size justification

The target sample size was determined by the two-tailed t-test power calculation. The estimated standard deviation of total oral morphine or equivalents is 20 mg. A difference of 10 mg between the two arms is considered clinically relevant. To detect a difference of 10mg of morphine (or oral morphine equivalents) between the experimental and control groups with a power of 80%, we calculated a target enrollment of 64 patients in each group. The null hypothesis is that the experiment and control groups will not have significantly different Post-operative Narcotic Usages in the first 48-hour period post-operatively. The alternative hypothesis is that the experiment and control groups will have significantly different Post-operative Narcotic Usages in the first 48-hour period post-operatively

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APPENDICES

APPENDIX A: **Participant Eligibility Checklist**

Protocol Title:	A Randomized Double-blinded, Placebo-Controlled Trial: Use of Transversus Abdominis Plane (TAP) Block in Breast Cancer Patients Undergoing Microsurgical Breast Reconstruction with Abdominal Free Flap
Protocol Number:	34315
Principal Investigator:	Gordon K. Lee, MD, FACS

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Female	☐	☐	
2. Greater than 18 years old	☐	☐	
3. Undergoing microsurgical breast reconstruction with abdominal free flap	☐	☐	
4. Has a prior diagnosis or presumed diagnosis of breast cancer or undergoing prophylactic treatment	☐	☐	
5. Capable of providing informed consent	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Allergic to local anesthetics or opioids	☐	☐	
2. History of addiction to narcotics within last 24 months	☐	☐	
3. History of chronic pain on opioids within last 24 months	☐	☐	
4. Specific mental health issues such as schizophrenia or bipolar disorder	☐	☐	
5. Pregnant			

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results,

radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	