Optimizing topical pain control for breast cancer patients undergoing preoperative radiotracer injection for sentinel lymph node mapping: a randomized clinical trial

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1. Project Summary

We plan a randomized clinical trial comparing four user-friendly, non-invasive topical pain treatments, including a novel thermomechanical distraction technique, for breast cancer patients undergoing radiotracer injection for sentinel lymph node mapping. There is significant variability in how practices approach minimizing pain with radiotracer injection. Patients have identified this procedure as particularly painful out of all the procedures they undergo related to breast cancer treatment. To date, no best practice approach has been identified that is easily implemented into clinical workflows across practice types. Our objective is to identify a practical and widely adoptable solution to this persistent problem and improve the experience of breast cancer patients starting their treatment trajectory within the health system.

2. Significance

Each year, over 270,000 American women will be diagnosed with breast cancer, making it the most common non-cutaneous malignancy in this population (1). The majority of these women have localized disease and will undergo sentinel lymph node (SLN) biopsy for cancer staging, as the presence of axillary lymph node metastasis is one of the most important prognostic factors for early stage breast cancer. Unfortunately, preoperative radiotracer injection for axillary SLN mapping can be extremely painful for some breast cancer patients, the pain of which is often severely underestimated by physicians (2). Indeed, radiotracer injection has been identified by some patients as the most painful experience in the operative day including surgery itself (3). The field of breast surgery has made large strides in improving patient experiences of breast surgery, including improving localization methods for breast conservation and incorporating regional blocks for the operative procedure. However, the pain with preoperative radiotracer injection remains distressing for patients. In order to enhance the experience of already anxious patients facing breast surgery, it is imperative that we identify methods to optimize pain control. Patient experience is an important component of the overall quality of health care and is essential for building positive relationships between patients and providers (4). These experiences and relationships are especially critical for breast cancer patients who are often only starting their treatment trajectory within the healthcare system.

3. Background

3.1 Periareolar radiotracer injection is the preferred method for SLN identification in breast cancer patients (5) but is extremely painful. In current practice, there is wide variability on pain management for radiotracer injection with no clear gold-standard. Intraoperative injection after initiation of surgical anesthesia would likely minimize pain the most. However, although some centers have successfully incorporated intraoperative injection of radiotracer into clinical flow (6–8), there are significant implementation challenges with this approach, including constraints associated with handling of radioactive material and coordination with nuclear medicine staff. For most centers, pre-operative injection is a necessity (8).

3.2 Prior studies have demonstrated that the injection of local anesthetic such as lidocaine significantly reduces pain associated with subsequent or concomitant radiotracer injection (9–11) **but may also reduce success of lymphatic mapping (Table).** While the reduction in pain scores with lidocaine injection is encouraging, studies have reported mixed results regarding success of SLN identification (9–11). The largest and most recent randomized controlled trial demonstrated markedly lower mapping rates for patients receiving lidocaine injections. Furthermore, some of the studies utilized special preparations of lidocaine along with the radiotracer, something not feasible for many

practices. As a result, many nuclear medicine radiologists and surgeons are uncomfortable using injectable lidocaine and instead rely on topical anesthesia for the radiotracer injection (12).

Table. Summary of Existing Literature on SLN Mapping Rates after Lidocaine Injections

Author	Design	Study years	Sample size	Method	SLN Mapping rates
Stojadinovic et al.	Randomized controlled trial	2006-2009	140	Prepared mixture of lidocaine and radiotracer (+/- bicarbonate) injected subarerolar	• 96% EMLA cream, • 97% sodium bicarbonate • 90% 1% lidocaine • 90% 1% lidocaine + sodium bicarbonate
Stearns et al.	Prospective cohort with historical control	Prospective 2011-2012 , historical 2005-2009	110 prospective, 187 retrospective	2cc of 1% lidocaine injected subareolar prior to radiotracer	• 95% 1% lidocaine • 94% historical control
Hawkins et al.	Randomized controlled trial	2009-2010	49	6cc of 2% buffered lidocaine injected subcutaneous	• 79% control • 72% 1% lidocaine + sodium bicarbonate

3.3 No topical anesthetic has been proven to be superior for controlling pain associated with radiotracer injection. Topical anesthetics such as lidocaine-prilocaine cream (EMLA) have limited benefit compared to placebo (13–16). To date, there have been no studies investigating the efficacy of an anesthetic patch (e.g. 5% lidocaine) or non-pharmacologic pain management for this procedure. Thus, there is still a need to investigate a practical, effective, and broadly adoptable intervention that will reduce the distress associated with preoperative radiotracer injection in breast cancer patients.

3. 4 Preliminary observations

Options for topical anesthetic: Institutionally and in the literature, EMLA cream does not appear to reduce pain with radiotracer injection (13–15). The nuclear medicine department at our institution discontinued the use of EMLA due to perceived lack of efficacy and workflow challenges associated with implementing EMLA application into practice (which may have impacted effectiveness).

The current standard of care at our institution is application of ice to the breast before radiotracer injection. Application of ice to the breast has not been directly studied in the setting of radiotracer injection, but ice and topical vapocoolant sprays have been found to reduce the pain of procedures such as venous and arterial cannulation in adults (17–20). According to breast cancer providers at our institution, patients continue to report significant pain with the procedure when ice is used as the topical anesthetic.

Lidocaine patches, in contrast to EMLA, are easier for patients and providers to apply and have demonstrated efficacy in neuropathic pain as well in aesthetic procedures (21–23). This represents a potential option for a topical anesthetic.

Novel intervention for procedural pain: Topical high frequency vibration combined with topical cooling is a novel method to alleviate acute procedural pain. It has been studied and implemented largely in the pediatric population. It is thought that mechanoreceptor and noxious thermal inhibitory stimulation alter normal pain conduction pathways and offers better pain control than cooling alone (24). This combined approach has been found to significantly reduce the pain and distress of venipuncture (25). This intervention is the most commonly used non-pharmacologic intervention for venipuncture pain within our institution's Children's Hospital with good anecdotal success in reducing pediatric pain. The literature in the adult population of combined vibration and cold therapy is much scarcer, but preliminary data suggests that this intervention is beneficial especially in those with greater pre-procedural anxiety and is superior to cooling alone (24). A combination of vibration and cooling has not been widely implemented in our adult population for any acute procedural pain, making it an underexplored and promising area of study. Our initial observations are that application of this type of vibration to the periareolar breast and even nipple areolar complex is tolerable.

4. Study Objective and Specific Aims

Primary Objective: To test the effectiveness of four alternative approaches to topical anesthesia on pain associated with radiotracer injection for women diagnosed with breast cancer undergoing sentinel lymph node mapping.

Secondary Objectives:

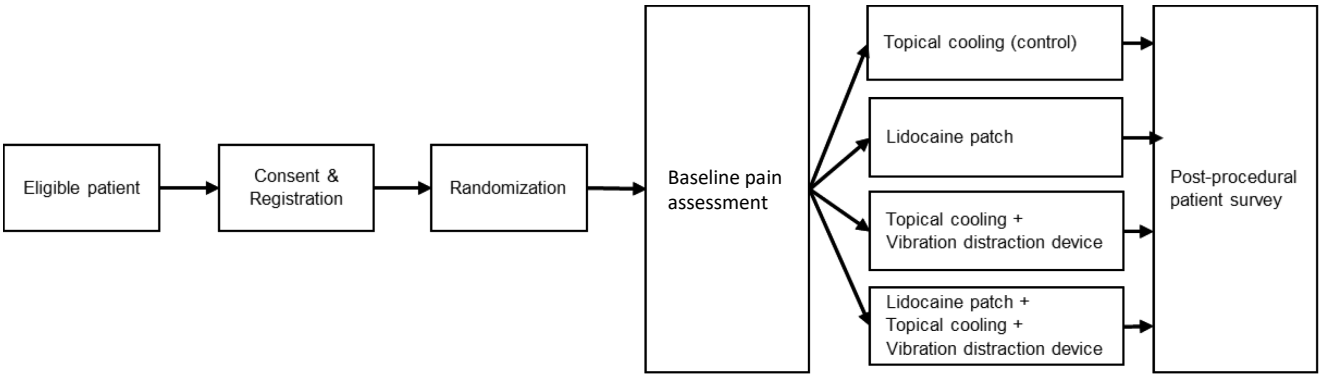
1. To assess patient satisfaction with pain control modality for radiotracer injection.
2. To identify barriers to implementation of the different pain control interventions.

5. Research Design and Methods

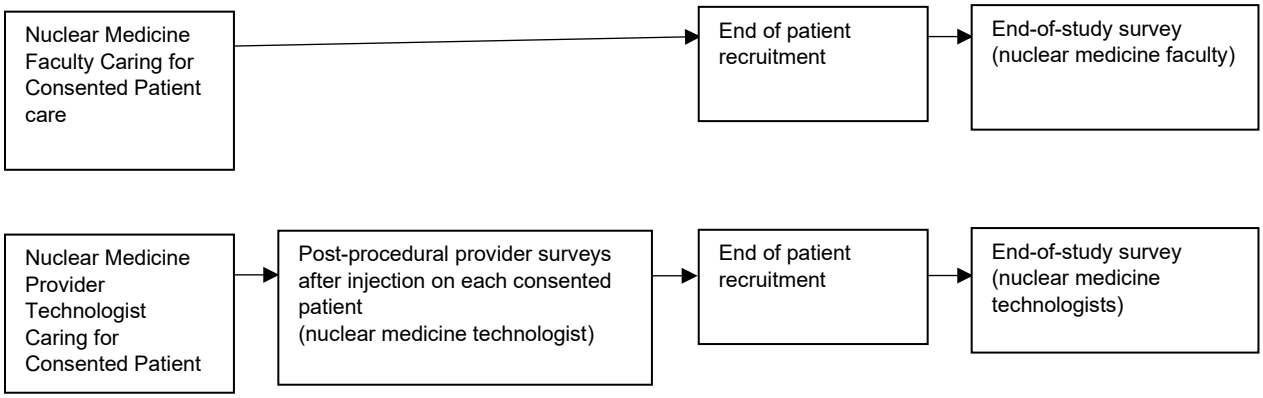
5.1 Study Overview and Schema

This is a randomized clinical trial testing the effectiveness of four alternative approaches to topical anesthesia for radiotracer injections for women diagnosed with breast cancer undergoing sentinel lymph node mapping. We will test two types of topical anesthetic (ice and lidocaine patch) with and without the addition of a topical high frequency vibration device (always combined with cooling). Ice is our control group as it reflects current standard of care at our institution.

Patient schema



Nuclear Medicine Provider schema



5.2 Selection of Participants

Inclusion criteria:

- ≥ 18 years of age
- biopsy proven breast cancer
- planned standard radiotracer injection (intradermal injection in the upper outer quadrant of the involved breast) for sentinel lymph node biopsy in the nuclear medicine department on the same day as surgery; standard versus non-standard injection is determined by the surgeon based on patient history at the time of procedure scheduling

Exclusion criteria:

- males
- pregnancy
- local anesthetic allergy or active use of the following medications
    - Abametapir (risk X)
    - Conivaptan (risk X)
    - Fusidic Acid (risk X)
    - Idelalisib (risk X)

    - Mifepristone (risk D)
    - Stiripentol (risk D)
    - Amiodarone (risk C)
    - Dofetilide (risk C)
    - Dronedarone (risk C)
    - Ibutilide (risk C)
    - Sotalol (risk C)
    - Vernakalant (risk C)

- Non-English speaking/reading
- Unable to provide informed consent
- Unable to participate with surveys
- Undergoing radiotracer injection the day prior to surgery or intra-operatively at the time of initial surgical scheduling
    - If patients are initially scheduled for same-day preoperative injection, complete all enrollment procedures (including randomization), and surgery is re-scheduled for a day prior to surgery or for intra-operative injection, they will be excluded if:
        - randomized to a lidocaine patch arm (Arms C or D)re-scheduled for an intra-operative injection
- Planned non-standard radiotracer injection site

5.3 Screening and recruitment:

Screening:

Introduction of the study: Patients being cared for by breast surgeons within the UW Breast Center will be eligible for consideration. Clinic schedules will be reviewed in advance by the study team to screen for patients meeting eligibility criteria. Breast surgeons will identify additional eligible patients and confirm eligibility of patients identified on study team screening.

Potential participants will be informed about the study by a member of their clinical care team at a standard of care visit or during a standard care phone call. Those interested in learning more will be contacted by a member of the study team to further discuss the study.

Recruitment:

The study team will offer all interested patients a study information packet (study information sheet, consent form, and baseline Wong-Baker FACES pain rating scale). Interested patients can receive the packet via email, mail, or in-person at a UWHC visit, according to their preference. Only study team members will provide these materials to interested patients and/or conduct in-depth discussion of the study. The study team will only email a link or electronic information packet after discussion of the inherent risks of email transmission of information and the patient has verbally consented to email receipt of this information.

Patients will be informed that final study eligibility will be determined based on the final scheduling of their surgical procedure, specifically whether the radiotracer injection is the same day as the surgery.

The study team will review the operating room schedules to identify patients undergoing standard preoperative radiotracer injection for sentinel lymph node mapping on the same day as breast surgery.

Interested patients who are fully eligible will be contacted by study team members to further discuss the study and consent. **5.4 Consent process:**

5.4.1 Patient consent
We request a waiver of signed consent and alteration of HIPAA authorization such that participant signature is not required for consent and authorization. Informed consent will be verbally obtained and documented prior to any research activities. After a patient expresses desire to enroll, informed consent will be obtained. Patients will have already received a copy of the informed consent and authorization document. If a new copy is required, this will be emailed or mailed to the patient based on their preference. If the patient will be at the hospital or clinic for another reason, they can also obtain a copy of the consent and authorization from the study team at that time. As much time as needed will be given for potential subjects to decide whether or not to participate in this study. Subjects will be informed that they are not obligated to participate in the study.

Waiver of signed consent:
The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Use of lidocaine patches and the Buzzy device for local pain control are not procedures that require written consent under non-research settings. Similarly, the surveys in this protocol present low psychological risk and would not require written consent under a non-research setting. The waiver of signed consent will not adversely affect the rights and welfare of subjects. The research cannot be practicably carried out without waiver of signed consent. Not all participants will enroll at the time of initial clinic visit. For patients who choose to enroll remotely over the phone, the short time between surgical scheduling and surgery date impedes their ability to return a signed consent before their surgery date and therefore formally enroll in the study. Subjects will be provided with a consent document to guide the informed consent process and will be given the opportunity to have all questions answered.

Alteration of HIPAA Authorization:
The use of protected health information involves no more than minimal risk to the privacy of individuals. Data privacy practices will protect identifiers from improper use and disclosure (see 11 Records to be kept, Privacy, and Confidentiality). Identifiers will be destroyed at the earliest opportunity consistent with research conduct. Participants will receive a consent and authorization document for their records detailing how protected information will not be reused or disclosed. Research cannot be practicably conducted without the alteration of HIPAA authorization. Not all participants will enroll at the time of initial clinic visit. For patients who choose to enroll remotely over the phone, the short time between surgical scheduling and surgery date impedes their ability to return a signed authorization before their surgery date and therefore formally enroll in the study. The research cannot be practicably conducted without access to and use of protected health information. Protected health information is required to access participant medical records for data elements of medical/surgical history and surgery data.

Consent can occur in one of the following ways:

1) In-person in the breast center: If the patient agrees to participate in the study after discussing with the breast surgeon and would like to undergo informed consent at the time of their clinic consultation, informed consent will be obtained in a closed, private room by a member of the study team at the Breast Center. A verbal consent and authorization will be obtained and documented. The patient will be given a copy of the consent form for their records. Patients will be informed that their final study eligibility will be determined after the surgery is scheduled and it is confirmed that the radiotracer injection will happen on the same day as surgery.
2) In-person at another location in the hospital or clinic: If the patient agrees to participate and has another appointment at the UW hospital and clinic, the study team can meet with the patient to obtain informed consent. The consent would be obtained in a closed, private location by a member of the study team. A verbal consent and authorization will be obtained and documented. The patient will be given a copy of the consent form for their records.
3) By telephone: The study team will review details of the study with the patient. Patient identity will be verified by verbally stated full name and date of birth. A verbal consent and authorization will be obtained and documented.

Subjects will receive a copy of the consent form and will be given contact information for study coordinator and PI for any additional questions.

5.5 Randomization:

After consent for enrollment has been obtained and eligibility confirmed, patients will be randomized to one of four intervention arms. Patients will be stratified by whether or not they are scheduled to undergo a breast radiology procedure (eg. wire localization, seed localization, elucent clip) prior to nuclear medicine injection. Treatment group allocation will be communicated to nuclear medicine providers with a colored paper printout that travels with the patient on the day of surgery.

5.6 Study procedures:

Intervention Arms

Intervention Group A (control and current standard of care)- Topical cooling: An ice pack will be applied to the upper outer quadrant of the areola/breast for 1.5 minutes immediately prior to radiotracer injection(s).

Intervention Group B- Topical cooling plus vibration distraction device application: An ice pack will be applied to the upper outer quadrant of the areola for 1.5 minutes immediately prior to radiotracer injection. For the last minute, the vibrating distraction device (Buzzy®) will be placed over the ice. The vibrating distraction device (Buzzy®) will be moved lateral at the time of the surgical prep but kept on the breast during the injection. In the event that a patient requires additional injections for adequate mapping, as determined by the image interpreting staff, the Buzzy® and ice treatment will be repeated prior to each additional injection.

Intervention Group C- lidocaine patch: A 4% lidocaine patch will be applied in the preoperative holding area to the upper outer quadrant at least 1 hour prior to radiotracer injection. Lidocaine

patches will be prescribed at the time of study enrollment. If a patient arrives for injection and does not have a lidocaine patch in place, they will be treated according to the standard of care (ice). In the event that a patient requires additional injections for adequate mapping, as determined by the image interpreting staff, the patient will receive the standard of care treatment (ice) prior to each additional injection.

Intervention Group D- lidocaine patch along with topical cooling plus vibration distraction device: A 4% lidocaine patch will be applied in the preoperative holding area to the upper outer quadrant at least 1 hour prior to radiotracer injection. The patch will be removed and the ice pack will be applied for 1.5 minutes prior to prep. For the last minute, the vibrating distraction device (Buzzy®) will be placed over the ice. The vibrating distraction device (Buzzy®) will be moved lateral at the time of the surgical prep but kept on the breast during the injection. Lidocaine patches will be prescribed at the time of study enrollment. If a patient arrives for injection and does not have a lidocaine patch in place, they will be treated with the Buzzy® and ice intervention prior to injection. In the event that a patient requires additional injections for adequate mapping, as determined by the image interpreting staff, the Buzzy® and ice treatment will be repeated prior to each additional injection.

Device:

Buzzy®: The Buzzy® device is IDE exempt under 21 CFR Part 812.2(c)(2) as an approved device being investigated in accordance with its labeling. Buzzy® has received FDA 510(k) clearance for pain control with injections. Buzzy® is a battery-powered device that produces high frequency vibration and is to be combined with a cooling element (e.g. ice pack) when applied to the skin for pain control. Buzzy® is thought to work by simultaneous stimulation of mechanoreceptor and noxious thermal inhibitory neurons which together modulate the transmission of pain.(26)

Drug:

Lidocaine patch 4% OTC: The patch provides 4g of lidocaine per 100g patch and is applied to the skin. This drug is exempt from IND 21 CFR Part 312.2(b)(1) as a lawfully marketed drug used in clinical investigation. This study is not intended to identify a new indication for the drug or for change in drug labeling. This investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. The dosage level used in the study is the standard dosage level of one patch of 4% lidocaine. The route of administration is the approved topical route of administration. The patient population in the study is not at increased risk from the drug related to any specific population factors.

5.6.1 *Surgical re-scheduling:*

If a participant is enrolled after meeting all eligibility criteria but the surgery is rescheduled, the participant's surgery date eligibility will be re-evaluated. If the participant is rescheduled for surgery with same-day preoperative nuclear medicine injection, then study procedures will be carried out per protocol. If the participant is rescheduled for surgery with intraoperative nuclear medicine injection, she will be withdrawn from the study as she will be unable to undergo study procedures. If the participant is rescheduled for surgery with a day-before surgery nuclear medicine injection she will undergo study procedures only if she was originally randomized to either the ice (arm A) or the ice + buzzy (Arm B) arms. If the participant is rescheduled for

surgery with a day-before surgery nuclear medicine injection she will be withdrawn from the study if she was originally randomized to either the lidocaine patch (arm C) or the lidocaine patch + ice + buzzy (Arm D) arms as lidocaine patches cannot be administered the day before surgery for logistical reasons.

5.7 Data Collection:
5.7.1 Patient-level data collection:
Patient surveys: Patients will complete one brief pain assessment and one survey during the study period.

Baseline pain assessment: Patients will complete a baseline pain assessment at the time of enrollment using the Wong-Baker FACES pain rating scale (Appendix A). The patients will have been given the Wong-Baker FACES pain rating scale at the time of their initial clinic visit. They will be referred to this scale during the enrollment phone call, and baseline pain score will be recorded.

Post-procedural survey: Patients will also complete a brief survey (<10 minutes) after the radiotracer injection but before initiation of anesthesia (Appendix B). Patients should complete the survey within three hours of receipt of radiotracer injection. This will either occur in the nuclear medicine suite or in the preoperative holding area with an iPad device or paper/pen. This post-procedural survey has intentionally been kept brief to decrease patient burden, which is especially critical as it will be completed on the day of surgery.

Chart review: We will record information including: age, race/ethnicity, medical history of chronic pain or fibromyalgia (yes/no), history of prior breast and axillary procedures (biopsy, surgery), history of prior breast cancer, active narcotic or other pain medication usage (over the past week, use of narcotics including tramadol at least twice weekly and/or daily use of Tylenol, NSAIDs, gabapentin, and/or amitriptyline), breast cancer laterality, tumor histology, grade and size, clinical and pathologic AJCC 8th edition cancer stage, hormone receptor status (estrogen receptor, progesterone receptor, Her2neu), and receipt of neoadjuvant chemotherapy. Additionally, we will record any pain medications taken on the day of surgery prior to the arrival to nuclear medicine (narcotics, Tylenol, NSAIDs, gabapentin, amitriptyline), the time of lidocaine patch application, breast radiology procedure prior to nuclear medicine injection, and sentinel lymph node identification on pathology report. We will also record type of radiotracer received.

5.7.2 Provider-level data collection: Nuclear medicine staff surveys: Nuclear medicine technologists will be asked to complete two sets of surveys. Nuclear medicine faculty will be asked to complete the end-of-study survey only.

Post-procedural survey: The first survey will be to assess the nuclear medicine technologists' immediate perception of the ease of administration of the intervention and the patient's post procedural pain (Appendix D). Each post-procedural survey will be linked to the patient study ID. This will be completed by the technologist assisting with each enrolled patient.

Nuclear Medicine Technologists will be providing ancillary and/or standard of care services that are within their normal scope of clinical practice. As part of their normal scope of practice and standard of care, technologists assist Nuclear Medicine MD, DOs with radiotracer injections and associated pain control/pain mitigation procedures. Technologists who assist with study participants will be included in the study team.

End-of-study survey: We will also administer a brief survey at the end of the trial to the nuclear medicine faculty and technologists involved in the radiotracer injection and associated pain control for patients on the trial. The nuclear medicine faculty and technologists will be the staff most consistently involved in the injections throughout the study time period and therefore would be most reliably able to reflect on implementation of the interventions. (Appendix E).

Nuclear Medicine faculty are ultimately responsible for and supervise each radiotracer injection and associated pain control. They serve an integral role in the conduct of research-specific study procedures and are included in the study team.

5.8 Schedule of Events

	Time of new breast cancer diagnosis	First clinic visit with breast surgeon	Telephone call after first clinic visit & surgical scheduling	Following radiotracer injection	Following final surgical procedure	Following study accrual
Assess inclusion/exclusion criteria	X	X	X			
Introduce study, offer participation		X	X			
Verbal consent and authorization)		X	X			
Baseline pain assessment		X	X			
Post-procedural patient survey				X		
Assessment of sentinel lymph node identification via chart review					X	
Nuclear medicine staff questionnaire				X		X

7. MEAUSRES

Primary patient outcome measure: The Wong-Baker FACES pain rating scale is a standardized 10-point Likert scale that is validated and has utility for patients with lower health literacy (27,28). It has been used in prior studies assessing pain with radiotracer injection for SLN mapping (9–11) (Appendix A).

Secondary patient survey outcome measures:

- Short Form McGill questionnaire: This is a validated pain questionnaire taking an average of 2-5 minutes to complete that captures subjective experiences of pain in both sensory and affective categories on a 4-point Likert scale. A total score out of 45 is calculated with sensory and affective sub-scores (29) and has been used in prior studies assessing pain with radiotracer injection for SLN identification (9–11) (Appendix B).
- We will ask questions to determine whether the patient received their intervention as assigned (Appendix B).
- Questions to assess patient experience and satisfaction were drawn from the following:
    - Consumer Assessment of Healthcare Providers and Systems (CAHPS®) questions Surgical Care survey (30) (Appendix B).
    - The American Society of Anesthesiologists Satisfaction with Anesthesia Questions (31) (Appendix B).
    - Studies of patient experience/satisfaction with local analgesia using validated surveys (32–34)(Appendix B)
- Recommendation of topical anesthetic option: We will ask patients whether they would recommend the topical anesthetic option that they received to others (yes/no) and inquire why or why not (open ended)(Appendix B).

Secondary staff outcome measures:

- Intervention usability and perceived patient pain:
    - The question to assess intervention usability is adapted from the Single Ease Question developed for assessment of usability after the completion of a task (31). The question addressing perceived patient pain utilizes the Numeric Rating scale (NRS), a validated pain rating scale used previously in provider assessment of patient pain with radiotracer injection (2,32). (Appendix C)
- End of study assessment:
    - The goal of the survey will be to assess experiences with implementing each arm of the study and any identified barriers. Nuclear medicine providers will be asked to rank order the usability and perceived efficacy of the different interventions. Space will be provided for open ended comments on benefits or barriers related to the interventions. (Appendix D)

8. Statistical Considerations

8.1 Analysis

Data will be analyzed with intervention arms masked. All scales will be constructed in a manner consistent with scale development, including item non-response. We will compare mean post-procedural pain scores (primary outcome) and other continuous secondary outcomes with ANOVA, testing the null hypothesis that mean post-procedural pain scores will not statistically differ between the control and intervention arms. Pairwise differences between each of the intervention arms and the control arm will be assessed with t-tests. Differences in potential control measures between patients randomized to the control and intervention arms that arise by chance will be examined using a chi-square test or Fisher's exact test for categorical variables and analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables (depending on distribution), respectively. Should there be significant differences in control measures between arms, an analysis of covariance (ANCOVA) will be used to assess the primary outcome, including significant covariates. Differences in the secondary dichotomous measures (sentinel lymph node mapping, patient recommendation) will be assessed with Chi-Square analysis. We will summarize responses to open ended questions in the patient survey and adherence to intervention. All analyses will follow an intention to treat approach. We will summarize the responses from the nuclear medicine providers/staff to determine what arm was perceived to be the most effective method for pain control and the easiest to administer. Secondary analysis will be performed on the type of radiotracer received and pain scores. **8.2 Sample size**

Power is calculated for our primary outcome variable, the Wong-Baker FACES pain scale. We assume patients randomly assigned to the control arm will have a Wong-Baker score consistent with scores reported for breast cancer patients in prior studies (mean=6.0, standard deviation=2.6) (10) and that the standard deviation across arms will be similar (2.6). A difference in 2 points in the Wong-Baker score between the standard care/control arm and the arm with the greatest reduction in pain score is considered clinically significant (27,37,38). A Monte Carlo power simulation of this one-way ANOVA design under an assumption of a sample with 40 patients per group, two point difference between usual care and the arm with the greatest difference, and alpha=0.05 yields 85% power to detect a difference of 2 points on the 10-point pain scale. Based on prior experience, we assume an enrollment rate of 60% (accounting for both declining to participate and drop-out after randomization) and plan to approach 270 patients and enroll 180 patients to allow for drop out to a target sample size of 160 patients.

9. Registration Procedures

Summary accrual information will be entered directly into the UW Paul P. Carbone Comprehensive Cancer Center OnCore database by the Study Coordinator.

A description of the clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

10. Risks and Discomforts to Research Subjects

Patients

Adverse reaction to pain control modality: Patients will be excluded based on presence of lidocaine or other local anesthetic allergy/contraindication. However, it is still possible that a patient develops an adverse reaction to placement of a lidocaine patch. Patients may also have a skin reaction or discomfort associated with other intervention arms. Currently, if patients do not tolerate ice pack application (the standard of care at the institution), it can be promptly removed. Likewise, patients will be encouraged to communicate any discomfort or intolerance of intervention arm, at which time the intervention can be easily and promptly discontinued. We anticipate any skin reaction to be self-limited.

Loss of patient confidentiality: This risk has been minimized through data protection efforts. These include storing data sheets used to collect the clinical information and paper questionnaires in a locked drawer within a locked office when not utilized. Data will ultimately be transferred into a password protected database stored on the Department of Surgery server. Only individuals directly involved in the development and analysis of the research project will have access to the data. After transfer of information from the data sheet to the database, all data sheets will be destroyed. No direct or identifying PHI will be included in the final analysis or final manuscript. Patients who wish to sign electronic consent and receive an electronic copy of the signed consent will be educated regarding the security risks of transmitting information via email.

Distress from survey questions: It is unlikely that patients will experience distress associated with the pain assessment or satisfaction/experience questions. However, patients will have the opportunity to contact study staff regarding any concerns that arise related to the survey questions.

11. Records to be kept, Privacy, and Confidentiality

All hard copy research files (including randomization lists, questionnaires, and data collection forms) will be kept in a secure, locked office in a locked filing cabinet and data will be transferred into a password protected computer and database stored on the Department of Surgery server. Only the minimum amount of patient and subject data that is necessary to achieve the aims of the research will be collected.

Patients: Directly identifiable information will not be collected on patient study questionnaires. To better protect patient information, electronic study data will be kept in two separate spreadsheets. The first spreadsheet will be a master code that includes the subject's name and medical record and an associated random study subject ID number. This subject ID will be kept in a password protected REDcap database on the Department of Surgery server (in a place separate from the data collection database). The data collection database will have the subject's ID number only, without subject (patient or provider) identifying information. When questionnaire data is then transferred into the database, only the subject ID will be included (no identifying information).

Only approved study personnel will have access to the identifiers (personnel approved for identification and recruitment and interaction with subjects will need access to update the master code/spreadsheet). Those who will not be interacting with subjects and/or who are only helping with analysis will only have access to the coded study data.
Nuclear medicine providers: Data from the nuclear medicine technologist post-procedure surveys will be linked to the patient subject ID. They will not contain additional patient-identifying information. These data will be stored on a password protected database on the Department of Surgery server.
After data analysis of the questionnaires is complete and the manuscript has been accepted for publication, all hard copies of research files will be destroyed. Other research materials and data are maintained in on the secure Department of Surgery server for a minimum of 7 years post publication. Data from this study will be stored for future research projects.

12. Data & Safety Monitoring
The PI and study team will be responsible for data and safety monitoring.

The PI and/or a member of the research team will be available to the patient for any questions or concerns related to the study. Standard quality assurance will be conducted prior to data analysis.

In accordance with federal regulations, the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the UW IRB policies.

13. References

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Appendix A. Baseline Pain Assessment

Note: this baseline assessment sheet will be provided to patients with the study materials so that it would be available for them to review over the phone.

Pain Control for Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy Research Study

Patient Baseline Pain Assessment

The following question will be reviewed with you if you decide to enroll in the study. It will be reviewed when a member of the study team calls you to discuss the study. Please save this paper to help with that discussion.

The following faces respresent a person who has no pain, or some, or a lot of pain. Indicate the face that shows the pain you are experiencing right now.

Appendix B. Post-procedural patient survey **Study ID_____**

Pain Control for Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy Research Study

Patient Post-Injection Survey

This survey has questions about what the injection of radioactive tracer was like for you. Your answers will help us learn what is the best method of controlling pain for this procedure.

The following faces respresent a person who has no pain, or some, or a lot of pain. Circle the face that shows the pain you experienced with the injection of radioactive tracer:

Study ID_____

Please fill out the following items about the pain you experienced with the injection of radioactive tracer. All questions about "pain" are asking ONLY about the pain you experienced in the breast with the injection and not other pain. Please answer questions about the pain you experienced in the breast DURING the injection, not other pain you may be feeling when you are filling out this form.

Check the column to indicate the level of your pain for each word, or leave blank if it does not apply to you.__

		Mild	Moderate	Severe
1	Throbbing	_____	_____	_____
2	Shooting	_____	_____	_____
3	Stabbing	_____	_____	_____
4	Sharp	_____	_____	_____
5	Cramping	_____	_____	_____
6	Gnawing	_____	_____	_____
7	Hot-burning	_____	_____	_____
8	Aching	_____	_____	_____
9	Heavy	_____	_____	_____
10	Tender	_____	_____	_____
11	Splitting	_____	_____	_____
12	Tiring-Exhausting	_____	_____	_____
13	Sickening	_____	_____	_____
14	Fearful	_____	_____	_____
15	Cruel-Punishing	_____	_____	

Indicate on this line how bad your pain is—at the left end of line means no pain at all, at right end means worst pain possible.

No Pain	_____	Worst Possible Pain

Study ID_____

The following are questions about the **pain control** you received for the injection of radioactive tracer. Please mark your answers with check mark(s) or circles.

1) Please mark with check mark(s) which of the following pain treatment(s) you received before your injection of radioactive tracer:

☐ Lidocaine patch on breast

☐ Ice on breast

☐ Vibrating device on breast

If you received a lidocaine patch, was it still on your breast right before your breast was cleaned for the injection of radioactive tracer?

☐ Yes

☐ No

☐ Not Sure

☐ Did not receive the lidocaine patch

Please answer questions 2-4 by circling the number that matches your level of satisfaction or dissatisfaction with different parts of your care for the injection of radioactive tracer.

How satisfied are you with:

	Very Satisfied	Satisfied	Somewhat Satisfied	Somewhat Dissatisfied	Dissatisfied	Very Dissatisfied
2) how the staff paid attention to your complaints like discomfort or pain with the injection?	1	2	3	4	5	6
3) the care provided by the staff performing your injection?	1	2	3	4	5	6
4) the pain control you received for the injection?	1	2	3	4	5	6

Study ID_____

5) Please circle the answer that matches your anxiety during the injection:

Very Anxious	Moderately Anxious	Slightly anxious	Not at all anxious
1	2	3	4

6) Please mark your answer to the following statement with a check mark.

I would recommend the pain control I received to others undergoing the same procedure.

☐ Yes

☐ No

☐ Not Sure

Why or why not?

Appendix C. Nuclear medicine staff questionnaire for post-procedural pain

Patient Study ID_____

Pain Control for Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy Research Study

Provider Survey for Post-Injection Patients

1) Did the patient arrive with a lidocaine patch on the breast?

☐ **Yes**

☐ **No but patient in a lidocaine patch treatment arm**

☐ **Not applicable- patient NOT in lidocaine patch treatment arm**

2) Did the patient require more than one radiocolloid injection?

☐ **Yes**

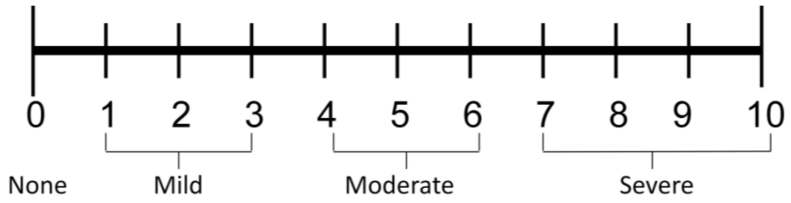
☐ **No**

3) Ease of administration:
Overall, how difficult or easy was it to administer the intervention? Circle a number on the 7-point rating scale below:

Very difficult						**Very easy**
1	2	3	4	5	6	7

4) Pain score of patient:
This question is interested in your perspective of the patient's pain intensity during the injection. Please do not ask the patient for a numeric pain score for the purposes of answering this question.

Please indicate on the following scale with an X where you think the patient's pain intensity was related to the radiotracer injection.



Appendix D. Nuclear medicine staff questionnaire upon study completion

Provider study ID _____

Pain Control for Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy Research Study

Provider End-of-Study Survey

The following questions are regarding the randomized study of topical pain treatments for the radiotracer injections for sentinel lymph node mapping in breast cancer patients.

1) Rank the following pain treatments in order of easiest (1) to administer to hardest (4) to administer. Use each number 1-4 only once.

   _____ Ice pack to the breast

   _____ Lidocaine patch to the breast

   _____ Ice pack to the breast with Buzzy

   _____ Lidocaine patch to the breast followed by ice pack to the breast with Buzzy

2) Rank the following pain treatments in order of what you think provided the best pain control (1) to what you think provided the least pain control (4). Use each number 1-4 only once.

   _____ Ice pack to the breast

   _____ Lidocaine patch to the breast

   _____ Ice pack to the breast with Buzzy

   _____ Lidocaine patch to the breast followed by ice pack to the breast with Buzzy

3) Please describe any challenges, if applicable, to implementing any of the pain treatments (open response):