The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A Practical Solution for Dyspareunia in Breast Cancer Survivors: a randomized controlled trial

Goetsch, et al

DOI: 10.1200/JCO.2014.60.7366

Date: Sept. 7, 2014

Re: *14-08664 - A Solution for Dyspareunia in Breast Cancer Survivors – A Randomized Controlled Trial*

This supplement contains the following items:

1. Summary of protocol changes between version 1 & 3:

a. Personnel Update: Addition of Aaron Caughey, MD, PhD.

b. Eligibility Criteria: Age increased to 70 years.

c. Eligibility Criteria: Decreased requirement from 2 years to 1 year from diagnosis of breast cancer.

d. Exclusion Criteria: Eliminated exclusion of never having used tampons.

e. Treatment Plan: Changed control product to saline from water and added height and weight for BMI calculation.

Treatment Plan: Added phone/email contact 6 months post enrollment to gather long-term acceptability and use information.

f. Study Procedures: Reduced open label (Phase 3) portion of study from 16 weeks to 8 weeks.

2. Final protocol (version 3.0).

Sincerely,

Martha Goetsch, MD

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OHSU Knight Cancer Institute
Treatment Protocol

Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #: 7630
Version 3.0

TITLE: Therapy to Prevent Sexual Pain in Menopausal Survivors of Breast Cancer

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Final Protocol Date: *Aug. 16th, 2011*
Protocol Revision Dates: *Dec. 15th, 2011*
Mar. 21st, 2012

SCHEMA

Study title: Therapy to Prevent Sexual Pain in Menopausal Survivors of Breast Cancer

Phase 1 (Screening for eligibility and pain touch tests)

Phase 2 (Randomization)

Phase 3 (open label drug treatment)

End of Study

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective: The objective of this research is to determine whether pain with intercourse can be reduced in breast cancer survivors and evaluate the effectiveness of a non-hormonal localized therapy.

1.2 Specific Aims:

Aim 1: To determine the specific site of vulvovaginal tenderness in menopausal breast cancer survivors who have entry dyspareunia. We hypothesize that the pain arises in the vulvar vestibule.

Aim 2: To determine whether a topical anesthetic at the vestibule is effective to prevent entry dyspareunia in breast cancer survivors. We predict that the localized use of lidocaine will be more efficacious than use of placebo liquid.

Aim 3: To determine whether women's quality of sexual life is improved by use of this local therapy to prevent pain with intercourse.

2. BACKGROUND

Breast cancer is the second most commonly diagnosed cancer in women.[1, 2] The National Cancer Institute reports that in 2007, there were 2,591,000 survivors of breast cancer. Estimates of the rate of dyspareunia pain with sexual intercourse in these women range from 40% to 100%.[3] Estrogen is known to be the most effective treatment for menopause symptoms, which include dyspareunia, but breast cancer survivors are instructed to avoid estrogen. Studies have confirmed that estrogen therapy for women with breast cancer increases the risk of cancer recurrence, especially in estrogen receptor-positive women.[4] Patients and clinicians are left with no safe, effective therapy. Thus, these 2.5 million women comprise a group needing a non-hormonal option to prevent pain with intercourse.

Pain with vaginal penetration is given the term "vulvovaginal atrophy" or "vaginal dryness" by most clinicians.[5] Clinicians recommend vaginal moisturizers, artificial lubricants, and regular sexual activity to correct vaginal dryness and painful intercourse, but oncology reviews of sexual dysfunction after breast cancer suggest localized use of estrogen as therapy,[6, 7] a seeming admission that there is no equivalent non-hormonal therapy. Oncologists vary in their leniency about estrogen use.

The field of vulvar pain research is emerging and offers a promising treatment for the problem of dyspareunia in women who lack estrogen. At OHSU in the Center for Women's Health (CWH), we have one of the few vulvar pain programs in the U.S. and the only one on the West Coast. The principal investigator (PI) is one of 3 specialists at the CWH who focus on this population. We see hundreds of women each year, and painful intercourse is their most common complaint. However, in national and international efforts in the field of vulvar pain, it is young, healthy women experiencing painful intercourse who have been the focus of research.

Women who complain of intercourse pain describe it as located at the entrance to the vagina and as a searing, burning sensation with any attempts at penetration. A physical examination finds exquisite

tenderness in the vulvar vestibule, the skin leading to the vaginal opening, in a narrow zone that is extremely painful to touch. Vulvar specialists refer to this pain as allodynia, exquisite pain provoked by what should not be painful at all. When the pain is severe, it prohibits any insertion into the vagina. The site of tenderness is much smaller than the pain would suggest.[8, 9] The International Society for Study of Vulvar Diseases terms the condition *vulvodynia*, specifically *provoked localized vulvodynia,*[10] since the woman feels no pain until touch provokes the pain. Vulvodynia has been highlighted in a 2010/11 NIH Appropriations Bill[11] and has been identified as "high-priority" by the Director of the Office of Research on Women's Health at NIH.[12] Also, Krychman[13] has called for a new emphasis on survivorship medicine and on sexual health programs for females with sexual dysfunction from cancer therapy. Further, the problem is not isolated: vulvovaginal atrophy (the term used by the American College of Obstetrics and Gynecology) is found in up to 50% of all menopausal women.[5]

The popular term *vaginal dryness* and the technical term *vulvovaginal atrophy* have been used for decades for painful intercourse. The term *vaginal dryness* presumes the cause of pain to be lack of moisture and the site to be vaginal, as that is how the less severe cases feel to women. *Vaginal dryness* implies an innocuous problem and influences the perceptions of patients and clinicians in both gynecology and oncology, perhaps explaining the dearth of research into this complaint.

Many artificial lubricants are marketed to facilitate comfortable sexual intercourse. In addition to lubricants, one over-the-counter product, Replens®, is a gel marketed as a vaginal moisturizer (WellSpring Pharmaceutical,Canada). A phase III study after breast cancer comparing a placebo gel, found Replens® to be equivalent to placebo.[14] Replens studies do not emphasize dyspareunia as an outcome since it does not ameliorate this symptom successfully.[15, 16]

Women of all ages coming to the Program in Vulvar Health with dyspareunia often use the popular terminology of *vaginal dryness* to account for their painful intercourse, but upon questioning, they describe the dryness as pain. At the Program in Vulvar Health, these women undergo an examination that encompasses the vestibule (entrance to the vagina) and the vagina, which are anatomically distinct. With a cotton applicator, surface tissues are lightly touched to check for tenderness (the cotton swab test). In vestibulodynia, the small area just outside the hymen but inside the labia is exquisitely tender. A liquid anesthetic is applied there for 1-2 minutes and the swab test is repeated. Lack of tenderness indicates that surface hypersensitivity (vestibulodynia) is present and rules out a problem termed generalized vulvodynia, a second cause of vulvar pain that is neuropathic and not peripheral. Once the vestibule is no longer tender, painless insertion of a speculum and a painless digital examination indicate a pain-free vagina. A visual assessment of the vagina may reveal a lack of moisture and thinned walls, but the site of pain is in the vestibule. This is the typical evaluation revealing menopausal vestibulodynia. In our proposed research, we will be performing this complete physical examination for each of our subjects (n = 50) to confirm the site of tenderness (Aim 1).

Research by several groups has confirmed that vestibulodynia is a disorder of too many pain nerves (termed *hyperinnervation*) at the skin surface in the vulvar vestibule.[17-19] While we and others are looking for the triggers of this nerve growth,[20-22] there is a need to relieve women of their pain. A non-hormonal therapy designed to target nerves may be efficacious in reducing painful intercourse, based on our findings of hyperinnervation and our decades of clinical experience. The increased pain nerves in the vestibule are the type known to be effectively targeted by local anesthetic agents that block sodium channels.[23] A therapy in use at the CWH for symptomatic relief of vestibule pain is lidocaine 4%, an anesthetic liquid for topical mucosal use. For women with vestibule tenderness that is reversible with

lidocaine, the clinician first shows the patient the site using a mirror, and then instructs her how to apply liquid lidocaine before intercourse. These women usually later report reduced pain upon intercourse. This therapy does not correct the increased nerve growth, and young women rarely consider symptom treatment alone to be satisfactory. Older women who have not had cancer can usually correct the vestibule pain via estrogen therapy, but patients who are cancer survivors are finding lidocaine to be practical and acceptable. We hypothesize that painful intercourse in breast cancer survivors is a form of vestibulodynia and is related to increased nerves in the vestibule rather than a vaginal-moisture problem. We predict that lidocaine will be an effective therapy to prevent pain with intercourse and our study compares it to a placebo, saline. Because breast cancer survivors with dyspareunia usually have such significant pain as to have stopped having intercourse, we will use a validated technique for women to judge the degree of vestibular tenderness without requiring the interactive feature of coitus. The Tampon test is a technique for judging vestibular tenderness and it has been validated as reproducible, specific and acceptable to women using it.[24] It has not been studied specifically in this group so it will not be the primary outcome measure. We will use pain measures suggested by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[25]

3. PATIENT SELECTION

3.1 Eligibility Criteria

1. Women aged 18 to 70 years old.
2. Has a previous diagnosis of breast cancer (ductal or lobular carcinoma, invasive).
3. 1 year from diagnosis of breast cancer.
4. Stable heterosexual partnership =/>5 years or by investigator discretion.
5. More than 6 months of consistent insertional pain with intercourse (may have stopped having intercourse due to this consistent experience of pain).
6. Menopausal, demonstrated by at least one of the following:
    i. cessation of menses for 1 years
    ii. Bilateral oophorectomy
    iii. FSH level >25 in women below age 50 with an ovary and scarred or absent uterus (acceptable FSH levels can be inferred if the woman's oncologist monitors FSH during aromatase inhibitor therapy).
7. Willingness to enter a study comparing a topical placebo liquid to topical liquid lidocaine.
8. Willingness to evaluate the liquids by use of a tampon test as many as 4 times per month, and willingness to attempt intercourse if the tampon test indicates tolerable penetrative pain.

3.2 Exclusion Criteria

1. Diagnosis of benign or malignant phyllodes tumor of the breast.
2. Consistently has pain in the pelvis or low abdomen during or after intercourse (deep dyspareunia).
3. Has developed shrinkage of the vaginal opening or vaginal length to the point of being too small to succeed in having vaginal penetration with the partner (will also be assessed at the clinical exam).
4. Partner has a problem of sexual dysfunction limiting his performance or making it inconsistent.
5. The potential subject or her partner has a serious current medical condition that might interrupt completion of a 6 month study.

6. Potential subject has been diagnosed by a physical therapist with significant pelvic floor muscle dysfunction causing pain (pelvic floor myalgia).
7. Potential subject has used topical or systemic estrogen within the last 4 months.
8. Has continued tenderness of vestibule mucosa immediately after application of both test liquids.
9. Allergy to lidocaine or other numbing agents.

4. TREATMENT PLAN

Once women qualify through initial screening, they will be scheduled for a screening visit at the Women's Health Research Unit (WHRU) (phase 1). Upon consenting to participate through informed consent, the PI will examine the subjects to ascertain the specific sites of their pain (Aim 1). Subjects will first be instructed to insert an un-lubricated cardboard-sheathed standardized tampon (Original Regular Tampax™) into the vagina and remove it and will rate their pain using a Numerical Rating Scale (NRS) with anchors of 0-10 reported to the study assistant. A visual examination by the PI will rule out vulvar dermatoses that might be a cause of dyspareunia (lichen sclerosus or lichen planus). The cotton swab test will be administered in the fashion published by the PI[9] but with eight sites. A moist small cotton-tipped applicator will be gently rolled over specific surfaces of the vestibule in a consistent pattern. Findings will be noted in the anterior vestibule at 2:00, 10:00, 12:00, in the para-hymenal vestibule at 12-3:00, 3-5:00, 6:00, 7-9:00, 9-11:00. Subjects will be prompted by the clinician to identify pain with non-specific descriptive words (e.g. annoying, stinging, burning) and the patient will provide a Verbal Rating Scale to the research assistant [(VRS) (none, mild, moderate, severe corresponding to A=no pain, B = irritative but not burning pain, C = moderate stinging, burning pain, D= severe burning, stinging pain]. Subjects will also be asked to rate pain at each site using the NRS. The research assistant will record each of these on a vulvar diagram that maps these sites. These comparative assessments will establish baseline data on menopausal vestibule sensitivity, something not specifically reported by vulvar specialists yet.

Next one randomly chosen clear liquid will be applied by the PI to allodynic skin surfaces (2+ or 3+ tenderness) for 3 minutes using one or more large or small cotton swabs. The OHSU Research Pharmacy will provide a 4% liquid lidocaine solution (FDA approved for mucosal surfaces) and a clear placebo fluid (normal saline). Study staff and subjects will remain blinded until the conclusion of phase 2 when the study becomes open label for the clinical learning portion of the study. The research pharmacy will allocate the randomization scheme to ensure blinding. Subjects and all study staff involved in the care of the participant will be blinded to study arm allocation. After the 3 minutes of liquid #1, a touch test will be repeated and the zones of allodynia will be mapped again, repeating the NRS and VRS. The second liquid will then be applied for 3 minutes and the touch test repeated and NRS and VRS recorded. The potential subject will either have developed numbness and will now have no pain with swab touch (indicating localized vestibulodynia) or they will still have some burning (indicating generalized vulvodynia) which excludes them from the study.

The examination will continue with speculum insertion for visual assessment of the vagina, for an assessment of pH using pH paper and collection of vaginal fluids and cells on a cotton tipped applicator for assessment after the examination is completed. The subject will be asked to rate vaginal pain on the NRS scale when the PI collects the vaginal fluid. The PI will perform a digital examination of the muscles of the pelvic floor in the manner used in the vulvar clinic as well as bimanual exam. Tenderness of the levator muscles will exclude the potential subject from phase II, the home-administered intervention phase of the study. Their findings up to this point could be used in the data set for

evaluation of lidocaine and the tampon test in an office setting, as these subjects have vestibulodynia. They could therefore complete the initial questionnaire for collection of further personal data but not go on to phase II of the study because of the confounding feature of pelvic floor myalgia, a cause of dyspareunia not addressed by lidocaine.

The vaginal sample will be assessed by microscopy for cell maturation in the following manner: one drop of Rakoff stain (5% light green and 1% aqueous eosin Y)[32] is added to a 2-mL suspension of vaginal cells. Examination differentiates, by color and morphology, parabasal cells (violet with a rounded shape and larger nuclei), intermediate cells (blue-green with larger nuclei), and superficial cells (red and leaf- like). A saline and KOH preparation will assess presence of leukocytes and fungal morphology in the vaginal secretions. A fungal infection or desquamative inflammatory vaginitis will exclude the subject, but other findings will be descriptive. Maturation and pH are included because we predict that our intervention will be therapeutic without changing the vaginal environment, thereby suggesting that "vaginal atrophy" is not the cause of dyspareunia. Atrophy that has caused shrinkage of the vaginal opening or vault will be assessed by bimanual examination. A vaginal aperture less than 2 fingers breadth at the hymen will exclude women unless they report that they can have full penetration with their partner.

Women who qualify at this point for enrollment after baseline physical assessment (Phase 1) will be shown their vestibule area with a mirror and instructed in application of liquid on a cotton ball to the posterior vulvar vestibule. This completes the patient's physical examination. During the first visit, subjects will fill out an Entry Questionnaire, noting their cancer, pain and obstetric/gynecologic histories. Additionally they will complete the Sexual Function Questionnaire (SFQ)[33], the McGill Pain Questionnaire-2 and the Female Sexual Distress Scale (FSDS). Subjects will be randomized to blinded home therapies (phase 2), using either 1) liquid lidocaine that subjects will apply at the tender genital locations just before penetrative touch, or 2) saline that subjects will apply at the tender genital locations just before penetrative touch. Lidocaine will be supplied as 4% aqueous lidocaine hydrochloride 50 mL bottles, manufactured by Roxane laboratories. Subjects will all be dispensed a supply of lubricant to be used for any at-home penetrative attempts after application of the study drug. Prior to any penetrative attempts subjects will be instructed to apply study liquid to the vestibule for 3 minutes. Subjects will agree to self-administer the tampon test after application of study liquid followed by lubricant at least twice per week for 4 weeks, and will be encouraged to attempt intercourse after application of study liquid followed by lubricant once weekly or more, if pain level permits. They will keep a diary of these activities and grade the amount of pain of each insertional attempt with the NRS. Before leaving the enrollment visit each subject will have blood drawn for an FSH and beta-estradiol level, and have their height and weight performed in order to calculate their body mass index (BMI).

At 2 weeks each subject will receive a phone call from the study assistant inquiring about any problems using the study liquid and whether they need any verbal explanation on where to place it.

After 4 weeks each subject will return for questionnaires (Visit 2 Questionnaire, SFQ, McGill Pain Questionnaire-2 and FSDS), diary review and examination #2 to reassess areas of tenderness, the vaginal maturation and pH, and the pelvic floor muscles. The examination will be as described above but with no blinded comparison of saline. All subjects will given 4% aqueous lidocaine to use prior to penetrative touch for the remainder of the study (phase 3) and will be encouraged to have at least once penetrative attempt per week. Subjects will be coached on proper use, with use of a mirror to facilitate understanding of the vestibular anatomy. Subjects will be encouraged to use the tampon test as needed

to confirm placement of the lidocaine prior to intercourse if they desire. Each subject will use lidocaine for the remaining 8 weeks of the open label portion of the study, keeping a diary that notes tampon tests, coital episodes and a pain assessment by NRS scale. Because subjects may need more guidance and specific instruction, they will able to return for visits as needed for 2 months. At month 3 the study will be concluded with a final examination (#3) and completion of questionnaires (Visit 3 Questionnaire, SFQ, McGill Pain Questionnaire-2 and FSDS). The final physical exam will evaluate allodynia, lidocaine reversal, vaginal maturation and pH and pelvic floor muscles. Data analyses will identify whether this non-hormonal therapy and clinical guidance was associated with increased coital intimacy and pleasure and increased quality of sexual life (Aims 2 & 3). We will also obtain subject permission for contact by phone or email in the near future (6 months post enrollment) to gather long term information about acceptability and continuation of product use, and quality of sexual life.

5. DOSING DELAYS/DOSE MODIFICATIONS

N/A

6. AGENT FORMULATION AND PROCUREMENT

6.1 Agent Accountability

The Investigator and Research Pharmacy Staff must maintain a careful record of the inventory and disposition of the study agent.

6.2 Study Agent being used is an FDA Approved Product and being used for an FDA Approved Treatment Method.

6.3 Lidocaine:

Availability: Study Agent is supplied to investigators by Roxane Laboratories

Product description: Xylocaine Topical 4% (lidocaine hydrochloride 4%)

Solution preparation*:* XYLOCAINE Topical 4% solution, 50 mL bottle.

Storage requirements: Study Drug will be stored at room temperature at CHH Research Pharmacy

Stability*:* Study Agent stable at room temp.

Route of administration: Topical solution

Expected adverse events:

Possible side effects of liquid lidocaine:

- Numbness where the drug is accidentally applied
- Redness or swelling of the skin at the application site
- Stinging or burning of the skin at the application site

- Skin irritation or itchiness at application site, immediately or hours later

Less likely, but serious side effects may include:

- Allergic reaction – rash, hives, itching, difficulty breathing, swelling of the neck area

Drug Interactions

- There are some drugs (prescription and non-prescription) that may increase the chance that lidocaine causes a minor reaction. The investigator will carefully review all of the drugs you are taking before allowing you to use the study drug. If any other health care provider prescribes any new drug(s) for you while you are in this study, please tell the investigator before you take the new drug. You could also have that provider talk to the investigator before prescribing the new drug. Do not take any new over-the-counter drugs while you are in this study unless you first check with the investigator.

7. CORRELATIVE/SPECIAL STUDIES

N/A

8. STUDY PROCEDURES AND SCHEDULE OF EVENTS

8.1 Study Visits

Visit 1: Screening & Enrollment

If subject agrees to participate in this study and meet all qualifications, they will be asked to come in for a screening visit. They will have study explained to them and sign the consent form before any study related tests are performed. The subject will fill out the Entry Questionnaire (demographics, cancer history, obstetric/gynecologic history). The investigator will conduct a series of exams to determine the site of the subject's pain. These exams are:

- A tampon test – the subject will insert and remove a dry cotton tampon into the vagina to assess whether it causes pain. They will be asked to chart their pain verbally on a scale of 0 (no pain) to 10 (worst possible pain).

- A cotton swab test – The investigator will roll a Q-tip over the surfaces of the entryway to the subject's the vagina and the subject will rate any pain responses as described in the Treatment Plan above

- Cotton swab tests after study drug or placebo is applied – The investigator will use a large Q-tip and apply either the placebo liquid or the study drug to the opening of the vagina for 3 minutes. The swab test will be repeated. The subject's verbal rating of pain will again be charted. After a pause the second liquid will be applied for three minutes and the swab test repeated. If tenderness has been noted and one of the liquids has corrected it, the subject will proceed for further screening.

- The investigator will perform a gynecological exam using a speculum for visual assessment of the vagina and she will collect a small sample of vaginal fluid and

cells. This sample will be microscopically analyzed to rule out common infections or disorders. A physical exam of vaginal muscles and a pelvic examination will conclude the screening process.

- Subjects found to be eligible for the intervention phases of the study (Phases 2 and 3) will be asked to fill out three separate study questionnaires:
    - Sexual Function Questionnaire
    - McGill Pain Questionnaire
    - Female Sexual Distress Scale

  Topics of the questionnaires include but are not limited to:

  Age
  Race
  Education level
  Obstetrics, gynecology, and medical history
  Breast cancer history
  Sexual activity/painful intercourse history

- After completion of the questionnaires, subjects will be randomized to one of two treatments; study drug or placebo on a 50:50 basis. The investigator will instruct the subject about how to apply liquid to the vaginal area. Subjects must agree to administer the study drug and then do a tampon test at least twice weekly at home for the next four weeks. Additionally, the subject will be requested to administer the study drug and attempt intercourse at least once weekly if pain level permits. Subjects will record these activities in a diary and chart the amount of pain experienced.

- At the end of this screening visit, a small amount of blood will be drawn to test hormone levels.

- All subject enrollment information will be sent to the Knight Cancer Institute (via Knight Subject Enrollment form) at the time of each enrollment to be entered into the Knight's surveyor database.

- Two weeks into Phase 2 the study assistant will call the subject to see if they are using the study liquid and whether they need verbal coaching on how to use it.

<u>Visit 2 (Week 4) – Start of Phase 3 of Study</u>

- The subjects will return for a clinic visit after 4 weeks of treatment at home At that time, the they will repeat the questionnaires and the investigator will complete another exam to reassess areas of tenderness.

- After examination and questionnaires are completed, all subjects (both placebo and lidocaine users) will receive unblinded study drug (lidocaine) to use for the remaining 8 weeks of the study. They will again be instructed on how to apply

study drug and will continue to keep a diary. Subjects will be given the option to return to the research clinic for the remainder of the study if they need additional study drug or further guidance and instructions.

Visit 3 – End of Study

- At the end of the 8 week period, the subjects will return to the clinic for a final visit. They will have a gynecologic exam and will another series of questionnaires. The gynecologic exam will be identical to the two previous examinations.

8.2 Early Termination

The subject may be withdrawn from the study for any of the following reasons:

8.2.1 Voluntary patient withdrawal
8.2.2 Investigator's decision that is in the patient's best interest to withdrawal
8.2.3 Noncompliance
8.2.4 Significant protocol violation
8.2.5 For any reason, at the Sponsor or Investigators discretion

8.3 Schedule of Events

Visit Procedure Table:

Procedures	Visit 1 (Screening)	Visit 2 (Intervention)	Visit 3 (Follow-up)	Additional intervention visits
Tampon Test	X	X	X	
Gynecologic exam	X			
Cotton swab test	X	X	X	
Two Liquid Tests	X			
Blood draw (4 mL)	X			
Cell Sample Collection	X	X	X	
Entry (Health) Questionnaire	X			
Sexual Questionnaires	X	X	X	
Dispense drug and application instructions	X	X		X
Dispense diary	X			
Diary review		X	X	X
Total time	90 min.	60 min.	60 min.	30 min.

9. MEASUREMENT OF EFFECT

All analyses for baseline assessment (phase 1) and randomized blinded intervention (phase 2) will be performed on an intention-to-treat (ITT) basis. We will examine the randomization by comparing patients' demographics and clinical factors such as dyspareunia by NRS, and sexual activity and psychosexual measurement between two assigned groups using Chi square and t-tests. Factors that differ between groups will be retained in subsequent analyses.

For primary analysis of pain outcome in Phase 2, mean NRS differences between treatment and placebo will be compared using t tests. The proportion difference in having intercourse will be compared with the Chi square test. After conclusion (of Phase 3) during which subjects have been asked to use lidocaine, paired t test for mean change and McNemar tests for proportional change will be used to analyze pain outcomes for the previous placebo users. Time effect of pain change will be explored graphically for all subjects and analyzed using mix effects mode for pain level change and generalized estimating equation (GEE) model for the ability to have intercourse. For secondary analysis of psychosexual measurements collected from validated questionnaires, mean differences in each domain or sum of scores from all domains will be compared between placebo and treatment groups using t test and the change over time for Phase 3 subjects will be analyzed using paired t test. If data does not meet the assumption of proposed methods, nonparametric methods will be applied. To determine whether the two groups can be combined into a single cohort, the outcomes after the initial placebo group is treated with lidocaine will be compared to those of the initial lidocaine group. Assuming these outcomes are not statistically different, the two groups will be combined into a single cohort. This prospective cohort will then be examined to determine various predictors of magnitude of success of treatment. It may also be examined to determine whether pain, functional, and quality of sexual life scores improve over time or actually regress back to initial evaluation.

Qualitative analysis for this study will be completed by noting repeating themes and grouping quotes to establish the frequency of shared themes. Questionnaires include open ended questions because this allows use of qualitative research techniques that can bring out themes not predicted by the questionnaire designer when closed choices are drafted. The PI has used qualitative techniques in the past in evaluating patients' responses to having the condition of vulvar vestibulodynia[28]. It is time-consuming to analyze but was purposely planned for this study.

Outcomes

We will identify the anatomic site of pain in our subjects. We expect that the anatomic site is small and in the vestibule, not the vagina (Aim 1). We will test the office use of the lidocaine test as compared to water as a diagnostic aid in confirming the peripheral locus of pain in vestibulodynia. We will test the predictive capacity of the tampon test which has not been tested in postmenopausal subjects. We expect that lidocaine will provide relief from pain in our subjects and that they will prefer lidocaine to placebo water (Aim 2). We will assess subjects' estimation of what this pain relief means for their quality of sexual life as cancer survivors (Aim 3). Our study will be an important step in translating expertise from the vulvar field to oncology. These preliminary findings may be used to further investigate whether hyperinnervation in the vestibule is the origin of pain in breast cancer survivors so that therapies designed to target these nerves can be developed.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

10.2 Informed Consent

Written informed consent will be obtained from all patients, or the legally authorized representative of the patient, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a patients signature cannot be obtained, and for all patients under the age of 18, the investigator must ensure that the informed consent is signed by the patients legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record.

10.3 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation.

10.4 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained indefinitely.

10.5 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/research/rda/irb/policies.shtml.

Fatal and life-threatening UP will be reported to OHSU IRB within 7 days of notification of the event. All other UP reports will be submitted to OHSU IRB no later than 15 days of occurrence or notification of the event. Copies of the report documents will be kept in the study regulatory binder.

UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU Knight Cancer Institute and IRB. Monthly accumulative reports will be reviewed by a DSMC Oncologist and forwarded to the CRRC.

10.6 MedWatch Reporting

For this investigator-initiated study, the investigator is considered the sponsor. The investigator is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug.

These adverse experiences will be reported using a MedWatch form 3500 for voluntary reporting. MedWatch forms. Instructions are available at www.fda.gov/medwatch . MedWatch reports can be submitted online at https://www.accessdata.fda.gov/scripts/medwatch/

When the serious adverse event is reported to the FDA, copies of the MedWatch 3500 form and supporting materials will be submitted to the OHSU IRB and the OHSU Drug Information Service. A copy of the MedWatch 3500 form and supporting materials will be kept on file in the study regulatory binder.

10.7 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each patient treated on this protocol. OHSU Knight Cancer Institute (CI), CRM shared resource is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on CI approved protocols according to the Data and Safety Monitoring Plan policies and procedures http://ohsucancer.com/crm

Locally initiated studies will be audited by an OHSU Knight CI DSMC audit team. Newly approved studies may be audited anytime after enrollment. Each OHSU Knight CI approved treatment protocol will be audited on an annual basis.

10.8 Inclusion of Women, Minorities and Children

10.8.1 Inclusion of Women and Minorities

No subject will be excluded from the study on the basis of racial or ethnic origin. Female and minority volunteers will be recruited for this study from the general population.
The projected gender composition of the study will include only women because the disease only affects women.

Table 1: Population Demographics - Oregon (100%)

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino			8.0
Not Hispanic or Latino			92.0
Ethnic Category: Total of all subjects*			100*

Racial Category			
American Indian or Alaskan Native			1.3
Asian			3.0
Black or African American			1.6
Native Hawaiian or other Pacific Islander			0.2
White			86.6
More than one race			3.1
Unknown/Other			4.2
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Complete Table 2. The numbers within Table 2 should reflect the anticipated recruitment of subjects. Each subject should be entered into the table twice: once under an ethnic category and once under a racial category. Do not inter "0" for any gender or minority category unless there is a protocol reason to exclude them. If the calculation is less that 1, enter 0-1.

Table 2: Projected Accrual for the Present Study *(enter actual estimates, not percentages).*

Ethnic Category	**Sex/Gender**			
	Females	Males	Unknown	Total
Hispanic or Latino	4			4
Not Hispanic or Latino	46			46
Unknown	0-1			0-1
Ethnic Category: Total of all subjects*	50			50
Racial Category				
American Indian or Alaskan Native	0-1			0-1
Asian	1-2			1-2
Black or African American	1-2			1-2
Native Hawaiian or other Pacific Islander	0-1			0-1

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
White	43			43
More than one race	1-2			
Unknown	2			
Racial Category: Total of all subjects*	50			50

10.8.2 **Inclusion of Children**

This protocol does not include children for the following reason: This study's objective is to treat postmenopausal women who are breast cancer survivors and are experiencing painful sexual intercourse. This does not apply to children.

1. STATISTICAL CONSIDERATIONS

11.1 **Study Objectives**

Primary Objective: The objective of this research is to determine whether pain with intercourse can be reduced in breast cancer survivors and evaluate the effectiveness of a non-hormonal localized therapy.

SPECIFIC AIMS

Aim 1: To determine the specific site of vulvovaginal tenderness in menopausal breast cancer survivors who have entry dyspareunia. We hypothesize that the pain arises in the vulvar vestibule.

Aim 2: To determine whether a topical anesthetic at the vestibule is effective to prevent entry dyspareunia in breast cancer survivors. We predict that the localized use of lidocaine will be more efficacious than use of placebo liquid.

Aim 3: To determine whether women's quality of sexual life is improved by use of this local therapy to prevent pain with intercourse.

11.2 **Baseline Comparability: N/A**

11.3 **Efficacy Evaluations:** Pain response scores filled out by subject during scheduled study visits.

11.4 **Safety Evaluations: N/A**

11.5 **Sample Size and Power:**

All power calculations used a 0.05 significance level and 2-sided test. The power calculation was made for the pain outcome in phase 2. A total of 50 patients will be recruited for phase 2 of the study; they will be randomly assigned for at-home therapy to either the treatment (lidocaine) or placebo (saline) group at an allocation ratio of 1:1 (25 in each group) using a simple randomization method. Allowing

for a 10% drop out rate, approximately 22 patients will remain in each group at the end of phase 2. This sample size will achieve 94% power to detect at least 15 points NRS mean difference between treatment and placebo with consideration of 10% placebo effect from a previously reported NRS mean ± std of 80 ± 14 for untreated patients.[34] The same sample size will also detect 50% difference in the ability to have more comfortable intercourse between treatment liquid (60% can) and placebo liquid (10% can) with 95% power using Z test with pooled variance. Patients in the placebo group will be offered treatment in phase 3 of the study. We allow for an additional 10% drop out by the end of phase 3, the remaining 20 patients in the groups will provide 99% power to detect mean NRS changes of 15 points compared to phase 3 entry using the paired t-test.

11.6 **Error Levels (alpha and beta) in Phase II studies: N/A**

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