Cover Page

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Women's Interventions for Sexual Health: WISH, A Pilot Study

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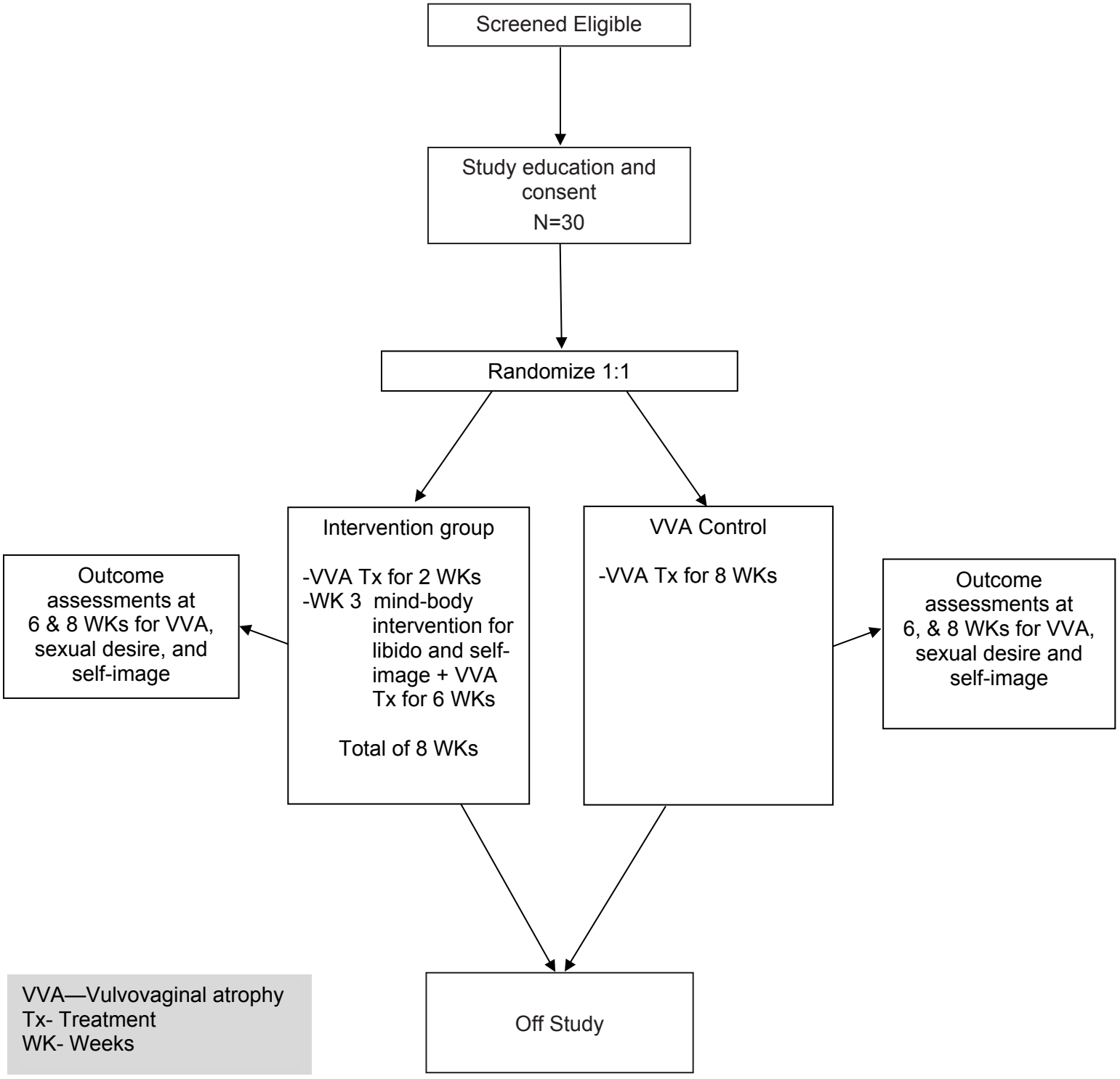
Study Schema



VVA—Vulvovaginal atrophy
Tx- Treatment
WK- Weeks

Study Summary

The overall objective of this program of research is to improve sexual health outcomes for women diagnosed with breast cancer. Our team is developing a multi-component intervention for the four key predictors of sexual health in female cancer survivors: self-image, vulvovaginal tissue quality and symptoms, desire/energy, and relationship-partner concerns. This proposal begins the proof-of-concept pilot study in women with a history of breast cancer to deliver a multi-component intervention to improve vulvo-vaginal atrophy with a vaginal moisturizer, and sexual energy and self-image with a mind-body intervention that involves relaxation and subconscious suggestions with a hypnotic induction delivered via audio file. The primary outcome will be to evaluate the feasibility and acceptability of a multi-component intervention for sexual function.

1.0 Objectives/Specific Aims

Primary Aim: Evaluate the feasibility and acceptability of a multi-component intervention for sexual function.

Hypothesis: At least 80% of randomized participants will complete the study without differential withdraws from the VVA control group.

Exploratory Aims:

Aim 2: Determine which measure (FSFI, ITS or PROMIS SexF) should be the primary outcome for this multi-component intervention for a larger, well powered randomized trial.

Aim 3: Determine the effect size to be able to adequately power a larger randomized trial.

This study is related to an NCI Moonshot priority (F) to minimize the debilitating side effects of cancer treatment. Completion of these aims will provide a critical foundation for NCI Cancer Prevention and Control Clinical Trials Grant Program R01 submission to implement a phase II or III randomized trial to implement in the NCORP network.

2.0 Background and Significance

Declines in sexual health in female cancer survivors

By 2030, the number of cancer survivors in the U.S. is expected to grow to nearly 22.1 million.[1] Breast cancer survivors represent almost a quarter of these cases, with the number of survivors at nearly 4 million in 2019 and growing to 5 million by 2030.

The long-term effects that are most strongly linked by evidence to a cancer diagnosis and treatment in female cancer survivors include hot flashes, night sweats, sleep changes, fatigue, and sexual health concerns, including vulvovaginal atrophy (dryness, and dyspareunia), changes in sexual functioning and negative self-image.[2-7] Specific challenges to the sexual response can consist of decreased desire, diminished arousal, decreased ability to achieve orgasm, and pain with vaginal insertion.[8-10] These physical symptoms can be cumulative and chronic without intervention due to the lack of estrogen and other sex steroid and neuroendocrine hormones. Symptoms associated with estrogen deprivation often contribute to distress, particularly post treatment, as the need to "get back to normal" is prevalent. Difficulties with self-image, mental health, and satisfaction or pleasure often accompany treatment effects creating emotional/psychological stressors.[9-11] Although mixed data exist about the role of relationship issues, [3,7,10,12,13] the physical and emotional challenges faced by survivors can impact the way a couple communicates and connects with each other as well as how each other's needs are met.[14,15] Intimacy can be disrupted, can be put on a hiatus while treatment takes priority or even avoided. Sometimes, without help, the couple may have trouble reconnecting once treatment is completed and life's routines are trying to return to "normal."

There is little debate that sexual health concerns and symptoms resulting from the cancer experience have complex etiologies that require education, support and overlapping symptom management.[16] Two recent editorials addressing two clinical trials evaluating pharmacologic interventions for libido (transdermal testosterone and oral bupropion) highlight the importance of developing trials that can simultaneously address factors to promote sexual health within the same study.[17,18]

To summarize, unlike chemotherapy related side effects like nausea which are transient, the physical effects to a woman's body, due to hormonal deprivation can be chronic and worsen over time without intervention and have the potential to negatively impact a woman's emotional adjustment and recovery from cancer. The profound interplay between these physical and emotional concerns/ symptoms necessitates interventions to be designed to address multiple factors simultaneously. Our team has developed a 4-pronged approach to promote sexual health targeting vulvovaginal tissue quality and symptoms, self-image, libido, and partner communication. In this study, we are testing two interventions that together address three of the aforementioned important concerns.

3.0 Preliminary Data

In this section, we will review the existing data for treatment of vulvovaginal atrophy (VVA), libido, and body image. These three components are the focus of this proof-of-concept study.

Vulvovaginal symptoms are consistently identified as predictors of sexual health concerns in female cancer patients and surviviors.[8,19-21] The vagina is highly regulated by estrogen and cancer treatments causing estrogen deprivation result in vulvovaginal dryness and discomfort, bleeding after intercourse, and increased susceptibility to infections, all of which can negatively impact enjoyment and interest in sexual intimacy.[22]

Standard/current treatment

The initial treatment for VVA symptoms focuses on non-hormonal treatments to improve tissue quality. Vaginal moisturizers, involving bases such as polycarbophil, hyaluronic acid (HLA), gums or gelatins, may be used on a regular basis for hydrating vaginal tissue. Moisturizers have been shown to stabilize vaginal pH in limited studies and demonstrated efficacy against VVA symptoms.[23] Ospemifene, a Food and Drug Administration-approved selective estrogen receptor modifier (SERM) for dyspareunia, is associated with potential adverse effects including hot flashes and venous thromboembolic events,[24] and has not been proven safe for women with breast malignancies. Water- or silicone-based lubricants are also suggested to decrease friction and enhance comfort with sexual touch and activity including vaginal insertion.

The gold standard in the general population if women do not respond to non-hormonal treatment is vaginal estrogen. Initially, the lowest dose possible (eg: 7.5 micrograms [mcg] suppository) is used to provide symptom relief while minimizing systemic effects. [24,25] Although very low dose vaginal estrogen may not result in systemic concentrations outside of the menopausal range, research has shown significant changes in lipids and bone biomarkers, suggesting systemic effects related to estrogen may indeed occur.[26,27]

Vaginal estrogens given to women on aromatase inhibitors (AIs) may be absorbed through the vaginal mucosa, resulting in significantly increased circulating levels and systemic effects.[28] Therefore for many women with a history of breast cancer, use of low dose vaginal estrogen is a last resort, reserved for when nothing else has been helpful.

In summary, data demonstrates that moisturizers applied to the vagina and vulva can be helpful over time if used frequently enough. A study done by Barton et al. evaluated vaginal DHEA compared to a bioadhesive moisturizer over 12 weeks which found that daily use of a simple moisturizer improved symptoms over 12 weeks with considerable improvement demonstrated by week 4.[23] A study comparing an HLA (non-hormonal) moisturizer to Premarin cream demonstrated significant improvement in both groups by 8 weeks with no difference between the two arms.[29] Therefore, we will use a non-hormonal moisturizer to improve the symptoms of vulvovaginal atrophy in this study.

Libido - Energy

There is a lot of controversy in the literature about what constitutes female sexual desire, often called libido.[30,31] It is clear that sexual desire/libido in women is multifactorial and more complex in comparison to men which appears to be more of a linear relationship between arousal and desire. In women, the relationship is not linear, and is confounded by vulvovaginal health, relationships and self-image.[32] It is also likely true that sexual desire may be more challenging in women with a cancer history compared to those without cancer. Specifically, the cancer literature supports that energy (perhaps fatigue) plays an important role in sexual health and declines as a result of a cancer diagnosis and treatment.[33] Data from our recent vaginal Dehydroepiandrosterone (DHEA) study demonstrate that at baseline, vitality explained 13% of overall sexual function (unpublished data). In addition, at baseline, women in our vaginal DHEA study reported vigor/energy levels right around the 50% point (53 out of 100 with higher numbers being better) on the vitality subscale of the Medical Outcomes Scale Short Form-36. Further, linear regression modeling of overall sexual function at baseline found vitality to be a significant predictor (p=.001) in addition to the variables of relationship, severity and bother of vaginal symptoms, and chemically induced menopause (unpublished data).

Studies have demonstrated improved libido for women who do not have a history of cancer with use of transdermal testosterone and flibanserin. Flibanserin is a relatively newly approved drug for hypoactive sexual desire disorder in premenopausal women. Studies in female cancer survivors evaluating transdermal testosterone[34] and a dopaminergic agent, bupropion,[35] have not demonstrated efficacy however. In the recently published bupropion study, baseline and 12-week values for the desire subscale of the FSFI were extremely low in the population of female cancer survivors who participated in this trial, in fact, lower than postmenopausal women diagnosed with hypoactive desire disorder who were included in the flibanserin trials.[35] Hence, this area of sexual health remains an important unmet need that will be addressed in this study. We propose to use a behavioral intervention, specifically, hypnosis shown to improve libido outcomes in a previous pilot study.[36]

Body Image

A comprehensive review of the literature between 1998 and 2010 succinctly summarizes the breadth and complexity of the issues surrounding sexual health in women after a diagnosis of breast cancer. The psychological issues of negative body image, such as feeling sexually unattractive, feeling a loss of femininity, increased anxiety, increased depression, and changes in one's sense of sexual self are noted.[19] A meta-synthesis of 30 qualitative studies representing 795 women supports the concept of "redefining self" in terms of body image and womanhood/femaleness as a pervasive, critical issue in the sexual health and functioning of women with breast cancer.[11] Estimates of the prevalence of body image concerns range from 31 to 67%, and the prevalence of those reporting arousal or interest issues is 46 to 56%, respectively.[11,12,37] Numerous studies, report direct effects on body/self-image in women with a history of breast cancer. In more sophisticated designs, body/self-image has been supported as a predictor of sexual interest and sexual health in general.[10]

There are limited, yet sufficient, data to support that psychosocial interventions targeting sexual self/body image are possible and have benefit.[38-43] In one study, participants were randomized to a 90 minute one-on-one session with a psychologist once a month for three months or to a wait list control to learn and practice mindfulness.[39] The intervention group significantly improved post treatment in every domain on the FSFI, except pain. These changes were large enough to be considered clinically important. The control group did not significantly change.[39] In a second study, women were randomized to six weekly 2-hour group meetings or to the control group that received printed educational materials. The intervention included education, communication training, and sex therapy. Although the groups did not differ significantly, the women who received the intervention reported greater satisfaction with sex.[41]

Our research team recently published a study that evaluated hypnosis versus progressive muscle relaxation for improvements in body image. The primary outcome was the breast impact of treatment scale that measures body change stress.[44] The study demonstrated that both arms improved significantly on this measure. Hypnotic techniques have a long history of being used for sexual dysfunction and ego/self-esteem strengthening.[45,46] The objective of the suggestions is to provide women with an improved sense of well-being, health, and positive self-image. In addition, suggestions are given around increasing ones' sense of control and the ability to manage physical and mental tension that have resulted in fatigue and apathy regarding sexual activity.[45] Imagery techniques can assist women in attaining, or re-attaining, a positive view of their sexual self. We will be using our hypnotic intervention from our previously published study in this two-component trial. Suggestions for sexual desire and energy will be integrated into the hypnosis in order to address both issues within one behavioral intervention.

Summary

This proof-of-concept study is the first step toward developing a well powered randomized clinical trial to evaluate the efficacy of a two-component intervention on three critical predictive variables of sexual function. This study intends to demonstrate a proof of concept that we can implement a two-step approach to address three areas of sexual function after cancer diagnosis and treatment: VVA, body image changes, and sexual desire/energy. All women will receive the same treatment for their VVA, and then be randomized to either arm 1: receiving hypnosis for body image and sexual desire after two weeks of VVA treatment or arm 2: VVA control group. The VVA control group will have the option to receive the hypnosis intervention after completion of eight weeks of the VVA treatment.

The potential for a comprehensive approach to sexual health improvement

This program of research builds upon work done by Ganz and colleagues. [4,5,9] They designed a comprehensive menopausal assessment intervention to address three symptoms (hot flashes, vaginal dryness, and urinary incontinence). Advanced practice nurses assessed each woman's needs and developed a tailored intervention including pharmacologic and behavioral interventions for these three main issues. At the time of this study, there was a paucity of effective interventions for these problems. Despite this, the investigators report significant improvements in sexual health as measured by the sexual summary scale from the Cancer Rehabilitation Evaluation System (CARES) in comparison to the usual care control group. The improvements were sustained at the two month follow up.[9] We are building on this multi-symptom, individualized approach, endorsed as a reasonable approach by others[47] and will target the three important symptoms shown to impact sexual health, specifically vulvovaginal atrophy, self-image, and sexual desire in this one proof of concept study.

The Team

Debra Barton RN, PhD, FAAN is a recognized expert in oncology symptom management and Vice Chair of the Cancer Control committee in NRG Oncology. Dr. Barton has had a rigorous program of research in the area of sexual health in cancer survivors. She has developed and implemented two clinical trials for libido (transdermal testosterone[34] and bupropion[35] and one for vulvovaginal atrophy[23] in the NCORP setting, involving multiple sites and hundreds of participants. Dr Barton will retire December 31, 2024.

Noël Arring, DNP, PhD, RN is an Associate Professor at the University of Tennessee, College of Nursing. Dr. Arring has over 17 years of clinical oncology symptom management experience. During her tenure at Mayo Clinic, she led the implementation of sexual health education for cancer survivors and clinicians. Since attaining her PhD in 2018, her work has primarily focused on clinical trials for oncology symptom management. She was most recently the operational University of Michigan site lead for 1R01AT009384-01A1 (Barton/Elkins MPI) Self-administered hypnosis for the management of hot flashes: a randomized clinical trial.
Carrie Lafferty, PhD is a Research Study Coordinator at the University of Tennessee, College of Nursing. She has 2 years of experience working with breast cancer survivors surrounding issues of sexual health and cancer symptom management and five years of project management and administrative support experience in health-related research.

4.0 Methods

4.1 Design

This will be a randomized two arm trial to evaluate the feasibility and acceptability (attrition), and effect size of a bio-behavioral, two-component intervention to improve vulvovaginal atrophy and self-image and libido. We will also evaluate the sensitivity and effect size of the chosen outcome measures to determine the best primary outcome for a larger, well powered randomized clinical trial.

4.2 Subject Recruitment

Recruitment and screening: Potential participants from the community will be identified in three ways: (1) physician referrals; (2) ResearchMatch.org; and (3) study advertisements including social media campaign, radio ads, flyers/brochures and a study website. Flyers may be posted in the greater Knoxville area. Locations such as churches, gyms, and cancer support groups. Brochures and flyers may be provided to physicians, providers, and organizations to distribute. IRB-approved recruitment materials may be posted on social media or in University of Tennessee/non-University of Tennessee newspapers, newsletters or websites, or read over WUOT. Participant eligibility will be determined using the Screening Eligibility Check List created from the criteria listed in 4.3.

Baseline visit: If a woman is screened eligible using the screening eligibility checklist, she will be mailed or emailed the consent form and scheduled for a virtual baseline visit. Baseline visits will be conducted using a HIPAA compliant platform (video or phone). The purpose of the baseline visit is to ensure that participants understand the study requirements, have their questions answered, be consented, complete baseline questionnaires, and are randomized. After confirming eligibility and reviewing the consent, eligible women will sign the consent using an IRB approved e-consent platform. After consent is attained, participants will be given a study number. Then baseline questionnaires will be completed, women will be randomized to vulvovaginal treatment with hypnosis starting in two weeks or vulvovaginal treatment control. Randomization will be done at the time of consent using a random number generator with “1” being the intervention group and “2” being the control group. They will then be educated about treatment with a vaginal moisturizer (see intervention details below). This treatment will begin within two weeks of completing the baseline visit (to allow for shipping of the moisturizer) and will be verified with the study coordinator. The start of vulvovaginal treatment will be confirmed by the study coordinator either through an email or phone communication with the participant. After confirmation of the start of vaginal moisturizer treatment, behavior education visit (Intervention) or follow up phone call (Control) will be planned for two weeks (+/- 3 days) for both groups.

Behavioral education visit: After treatment for vulvovaginal dryness has been underway for two weeks for the intervention group and VVA control group, a second remote visit will be conducted to assess how the vaginal treatment is progressing and to answer any questions about use of the moisturizer and assess for any adverse events. Also, during this second remote visit, the intervention group will be educated about the hypnotic induction intervention (see intervention information below). The rationale for splitting this education into a second visit is two-fold. First, doing it during the baseline visit would make that visit too long and too complex. It is likely participants would be overwhelmed with all of the information. Secondly, since the treatment for vulvovaginal

atrophy will take eight weeks for large effects to be seen, it is important the treatment get started and women get into that routine before adding a behavioral component. It is a standard approach in complex behavioral change to take a stepwise approach.

Phone follow up calls: Participants in both groups will have follow-up calls every two weeks (+/- 3 days) during the intervention except the week of the behavioral education visit to assess for adverse events, problem solve any lack of adherence, ensure completion of data collection and enhance study engagement.

A Screening and Enrollment Log will be maintained to document eligibility/ineligibility, screen dates, consent dates, and referral source of each individual screened.

4.3 Subject Selection

This feasibility study will focus on breast cancer survivors because substantial data demonstrates a high prevalence of sexual dysfunction in breast cancer survivors[8-10] and this population has been found to be helpful in providing feedback about interventions and their experience.[48,49]

4.3.1. Inclusion Criteria

1. Age ≥18 female
2. History of breast cancer, stages I, II or III
3. Completed primary treatment (chemotherapy, radiation and/or surgery) ≥ 3 months and ≤ 5 years prior to registration
4. May use concurrent adjuvant endocrine therapy or HER2-targeted therapy while on study
5. May use topical products (e.g., lidocaine) vaginally prior to penetrative vaginal sex
6. Ability to read and write English
7. Able to engage in sexual activity
8. Currently has a sexual partner
9. Responds “yes” to “Do you currently experience vaginal or vulvar dryness and/or pain with sexual activity?”
10. Responds “yes” to at least one of the following questions:
    - “Have you experienced negative changes in your body image since being diagnosed or treated for cancer?” or
    - “Have you experienced negative changes in your sexual desire since being diagnosed or treated for cancer?”

4.3.2 Exclusion Criteria

1 Antidepressants are allowed if a person has been on them for 30 days prior to registration, and dose or treatment is not expected to change
2 Past history of sexual abuse
3 Psychiatric disorder such as major depressive disorder, bipolar disorder, obsessive compulsive disorder or schizophrenia. (Defined per medical history and/or patient self-report)
4 Currently enrolled in another study that addresses sexual health (enrollment in other clinical trials will be allowed)

5 Use of oral, transdermal or vaginal estrogen is not allowed while on study

4.4 Intervention Group

The entire length of the study intervention will be eight weeks with the first two weeks treating only vulvovaginal dryness and then adding treatment for body image and libido for an additional six weeks while continuing to treat the vulvovaginal atrophy.

Vaginal Moisturizer

Vulvovaginal dryness will be treated with a daily moisturizer for two weeks, then every other day for the remaining six weeks. Vaginal moisturizer will be applied at night, before sleep and after all sexual activity. Several moisturizers are available, including vaginal DHEA (IntraRosa®). Due to the need for reproducibility, we have decided to use one non-hormonal vaginal moisturizer, Replens™ moisture, which is a vaginal moisturizer consisting primarily of a purified water, glycerin, and mineral oil. Other ingredients included in the formulation are polycarbophyl, carbomer, homopolymer type B, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide. The moisturizing gel was determined to be a medical device for marketing by the FDA in 2010. It has been studied in limited populations[50,51] and shown to have efficacy in treating vulvovaginal atrophy. It is non-hormonal (unlike vaginal DHEA) and therefore will be more likely to be acceptable by a broader range of oncology providers.

Hypnotic Relaxation Intervention: a behavioral treatment for body image and libido

The hypnotic relaxation intervention consists of three different audio files. Each audio file will be used 3 times per week for 2-weeks. These three hypnotic inductions build upon each other. Each hypnotic induction is about 20 minutes in length. The first hypnotic induction audio consists of focusing on relaxation, feelings of wellness, wholeness, strength, and confidence. The second hypnotic induction audio focuses more specifically on body image related to sexuality and being a sexual being. The third hypnotic induction audio focuses on sexual desire, passion, and energy.

Audio I: Hypnotic relaxation for deepening relaxation and a sense of well being
Perform a hypnotic induction to address self-love and enhance relationship to self; experience deep relaxation and suggestions for a sense of wellbeing. Used during study weeks 3 and 4.
Goals:

- Experience an increased sense of relaxation
- Experience improved feelings about their body
- Experience feelings of comfort and well being

Audio II: Hypnotic Relaxation for Improving Self Image Awareness
Perform a hypnotic induction to focus on improving body-image; suggestions for visualizing a body as strong, healthy, and beautiful. Used during study weeks 5 and 6.
Goals:

- Increase relaxation

- Build on positive feelings about your body
- Improve feelings about your sexuality
- Improve sexual experience

Audio III: Hypnotic relaxation for sexual desire and energy
Perform a hypnotic induction to improve desire for intimacy and experience increased energy and sense of wellbeing. Used during study weeks 7 and 8.
Goals:

- Increase relaxation
- Build upon improved feelings about your body
- Build upon improved feelings about your sexuality
- Improve sexual desire and energy

VVA Control

The VVA control group will get the eight weeks of vaginal moisturizer exactly as described above for the intervention group. After completion of the eight weeks of the study, the women assigned to the VVA control will be offered the Hypnotic Relaxation Intervention to complete on their own off study.

Accrual: Our research team has successfully recruited cancer survivors into clinical trials with an average of 4-6 per month. Weekly and monthly accrual goals will be set and achieved through a multipronged recruitment approach.

4.5 Time and Events Table

Table 2. Schedule of Participant Activities (All study contact is virtual)

Activities			Treatment and Assessments							
	Screening	Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Study Education										
Consent										
Screening Check List										
Demographic Information Form										
Outcomes										
Female Sexual Function Index full scale										
FSFI subscales: pain, dryness, desire		Included in full scale								Included in full scale
Impact of Treatment Scale										
PROMIS® Sexual Function and Satisfaction										
Current vaginally applied topical products										
Hypnosis practice log					*	*	*	*	*	*
Adverse Events										
Follow up Phone Calls										
Conditions										
Intervention		Vaginal Moisturizer								
		Hypnosis								
VVA Control		Vaginal Moisturizer								

* Intervention group only

5.0 Measures

Feasibility: We will keep spreadsheets of the numbers of women who receive a full eligibility screen and how many of those are found eligible versus not eligible, and of those eligible, how many consent to participate versus decline participation. The analysis and definition of what is considered feasible is in the statistical analysis section.

Acceptability: We will keep records of the number of women who complete the protocol, including the questionnaires at all data points versus those who do not complete either the protocol treatment, the questionnaires, and/or both. The analysis and definition of what is considered feasible is in the statistical analysis section.

Adherence: We will keep the following data to determine adherence to various aspects of the study: a) Number of missing questions within questionnaires; b) number and type of missing questionnaires; c) number of women who use the moisturizer exactly per protocol; d) number of women who use the moisturizer at least 80% of the time described by the protocol; e) number of women who use the moisturizer less than half of the time described by the protocol; f) number of women in each arm who listen to each audio sessions at least once in the assigned two week period; g) number of women in each arm who listen to each audio session at least once per week; h) number of women in each arm who listen to each audio session more than once per week.

Demographic Information Form: a brief medical history that obtains age, gender, sexual orientation, race/ethnicity, education level, marital status, cancer diagnosis, and similar demographic information. In addition, any other medical conditions that would exclude possible participants will be captured with this form.

Hypnosis Practice Log: Frequency of home practice is thought to be one of the moderators of the efficacy of hypnosis interventions.[52] Participants in the hypnosis group will be given a log to be completed weekly. The log will provide space to put the date, whether or not the participant listened to their audio recording, the number of times they practiced, and provide a space for comments about any interruptions or barriers to listening to the recordings.

Current topical (e.g. lidocaine or vaginal moisturizer) products will ask which products (if any) participants used vaginally within the last 2 weeks.

Female Sexual Function Index is a relatively brief measure (19 items) that has been developed and validated to be used across the age range of women, including postmenopausal women.[53] Its conceptualization came out of an evolving understanding of female sexual functioning in recent years. It is a multi-dimensional measure that covers the major domains of female sexual functioning including desire, arousal, satisfaction, and orgasm. Additionally, it addresses lubrication and pain. Its discriminate validity is based on its ability to differentiate women diagnosed with female sexual arousal disorder from normal controls. The FSFI looks at measures of both frequency and desire in each domain as well as satisfaction in most domains. The desire subscale consists of two items and has a range of 1.2 to 6 when scored. A cut off for less than normal desire has been determined to be less than 3.3. The FSFI has been used in both intervention and epidemiologic studies. The FSFI has been validated across a wide range of sexual problems, with the most recent Cronbach alpha's being over 0.9 for internal reliability. A score of 26.55 (from a range of 2 to 36) was found to be the cut point to distinguish women with and without sexual dysfunction (lower scores indicating sexual dysfunction). The FSFI was

used in the Alliance N10C1 study that accrued mostly women with breast cancer.[54]

Impact of Treatment Scale is a measure of body change stress and was developed by investigators at The Ohio State University. It was developed and tested specifically in women with breast cancer. It has demonstrated good reliability and validity in both samples, with Cronbach alphas over 0.90. It was able to discriminate between women with lower and higher satisfaction with their sexual life.[44]

PROMIS® Sexual Function and Satisfaction V2.0 (PROMIS SexF V2) measures sexual activities, symptoms, functioning, and evaluation of sexual experiences.[55] General screener items ask about sexual activity and reasons for not having sexual activity in the past 30 days. Researchers are encouraged to select the sexual function and satisfaction domains and items that are relevant to the specific sample being studied. Participants will answer the 14-item version that includes screener items, items asking about interest in sexual activity, lubrication, vaginal discomfort, clitoral discomfort, labial discomfort, orgasm and pleasure, and satisfaction. In this instrument, higher scores indicate more of the thing being described by the domain. Reliability and validity have been demonstrated in multiple studies. In the validation study, Cronbach's alpha scores ranged from 0.85 to 0.98.[55] This measure has been used in other studies of dyadic sexual health interventions with similar reliability and validity.[56]

6.0 Procedures

6.1 Data Management

The baseline and outcome-related questionnaires will be administered online via an HIPAA compliant platform such as Qualtrics or RedCap and/or via a paper collections process.

All materials collected are for research purposes only, and data will be kept in strict confidence. No information will be given to anyone without permission from the participant. The consent form includes the informed consent statement required by the University of Tennessee IRB for studies involving human subjects. This statement guarantees confidentiality and identifies the subject as the owner of the information received. Identifying information will be kept separated from study outcome data provided by participants through the use of study identification code assigned to each participant. Any identifying information that is collected on paper will be kept in a secure location within a locked file cabinet separate from the participant data charts.

Analyses will be de-identified and include only summaries of data.

6.2 Vaginal Moisturizer Distribution

Study staff will send Replens™ vaginal moisturizer to all participants. Receipt of Replens™ will be confirmed by study staff via phone call or email with participant before the agreed upon week 1 start date. The distribution of Replens™will be tracked with a log detailing participant study ID, date product was sent to participant, date product was delivered to participant according to tracking number and date participant confirms receipt of Replens™ moisturizer.

7.0 Data Analysis

The data will be summarized using descriptive statistics (mean, standard deviation, median, percentage, and frequency). The demographic and clinical characteristics including FSFI, BITS, PROMIS SexF V2, and adverse events will be descriptively analyzed with effect size calculations done for the validated quantitative measures. All statistical analyses will be completed using either SPSS or Stata.

7.1 Analysis Plan

Aim 1: Evaluate the feasibility and acceptability of a two-component intervention for sexual function.

Feasibility will be evaluated through determining the accrual rate and screen failures. Acceptability will be determined by retention rates.

Accrual rates will be calculated by determining the number of women per month who consented to participate in the study divided by the number who were eligible and educated about the study.

For purposes of this study, screen failures will be calculated as the number of women for whom full eligibility criteria are evaluated using an eligibility checklist and initial screening call and who are determined to be ineligible through that call.

Retention will be calculated as the number of women who complete all eight weeks of the study and complete the FSFI at baseline and eight weeks divided by the number who are randomized and begin study treatment.

Conversely, attrition rates will be calculated by dividing the number of women who do not provide FSFI endpoint data for all data points by the number of women who are randomized and begin study treatment. Attrition rates of 25% or less will be considered feasible. Withdrawal reasons will be captured and reported by category.

Adherence: Adherence will be determined by calculating the number of women who begin study treatment who have at least an 80% compliance with study treatment related to the vaginal moisturizer and behavioral education materials.

This study will be determined to be feasible and acceptable if we have at least a 60% accrual rate; 80% retention rate and an 80% adherence rate (d+h under adherence).

Aim 2: Determine which measure (FSFI, ITS or PROMISE SexF) should be the primary outcome for this multi-component intervention for a larger, well powered randomized trial.

For all of the patient reported outcome measures, we will calculate missing data rates, change from baseline to each data point, and look at how variable measures are over time. This information, along with effect size data discussed in Aim 3, will be considered in determining the optimal measure to use for the primary outcome in a larger trial.

Criteria we will be looking for in a “winning” measure includes: a lack of missing data on any items; smaller “placebo” response, evidence of a better linear trend over time, and sensitivity to change.

Aim 3: Determine the effect size to be able to adequately power a larger randomized trial.

Effect sizes, Cohen's *d* or *f,* will be calculated for from baseline to week 8. Effect sizes will be calculated for both study arms for the PROMIS, FSFI total score; FSFI lubrication, pain, and desire subscales and the Impact of Treatment Scale. Means, variance, and 95% confidence intervals will also be calculated to better estimate what sample size is needed for a larger trial with at least 80% power to detect at least a medium effect size.

7.2 Power Considerations

Since this is a feasibility study our main outcome is to assess accrual, retention, attrition, measure sensitivity, and effect size for the multi-component intervention. A sample of 15 participants per arm will allow us to design estimates that we can use for the development of a larger study.

8.0 Protection of Human Subjects

8.1 Sources of Material

The sources of material include data obtained from questionnaires. Data collected from participants will include the standardized questionnaires as described in the research plan. Additionally, participants will be asked to provide demographic and contact information. All data are collected for research purposes only, as part of the proposed study. All data will be kept completely confidential and referenced only in terms of a coded research assigned number. Data will be entered into a statistical database (SAS, Stata or SPSS) that is password protected and accessed on a hard drive protected by a fire wall. A unique study number will be given to each participant. This will ensure the confidentiality of the participants.

8.2 Potential Risks

Study visits and forms: Participants may be inconvenienced by the completion of forms, phone calls, and virtual study visits. We will make every attempt to work around the schedules of participants and to minimize burden on patients with respect to forms and follow up phone calls.

This study presents minimal potential risks to participants. Participants may choose to not participate in any part of this voluntary study. Potential risks include agitation and anxiety which we will try to minimize by ensuring participants understand how to use the intervention including additional relaxation exercises included in the study materials. Participant may have discomfort during completion of study questionnaires, frustration with the intervention due to lack of perceived benefit, which we will try to minimize through participant education on the purpose of the study. Further, with the vaginal moisturizer, participants may develop a vulvar rash or irritation; they may experience burning or itching; or they may experience a vaginal infection.

Risks associated with this trial will be kept to a minimum and all participants will be monitored carefully. Patients will be reminded that they can discontinue study participation at any time they choose or if their primary doctor feels it is in their best

interest to stop. Participation in this research study is strictly voluntary. The participant may opt to withdraw consent at any time for any reason. The investigator will notify the participant of any new information related to risk, toxicity, or efficacy that could influence the decision by the participant or investigator to continue study therapy.

Confidentiality: Any information about the participant obtained from this research will be kept confidential. Participants will not be identified by name in any publication or presentation resulting from the study. A code will be assigned to each participant that will allow for tracing the identity of each study participant. The IRB and Data Safety and Monitoring Committee will assess confidentiality and safety throughout the study period. Participant data will be stored using UTK encrypted servers and/or in locked files. Only IRB approved research staff will have access to participant files. All data will be de-identified and coded with study numbers.

Research team members are trained in the intervention and work directly under the supervision of Dr. Arring and Barton. Measures will be taken to ensure each participant understands their right to withdraw from the study at any time for any reason. Participants will be gently coached using behavioral change theory to implement their assigned study treatment as designed but at no time will participant be made to feel guilty about or pressured to implement the study procedures in any way. If the research therapists assess at any time that study participation is causing an undue burden on a participant, they will address this issue and again assure the participant of their right to withdraw.

Participants will be notified of any potential breach of personal information, should it occur.

All study records will be retained per institution policy.

8.3 Compensation for Participants

Participants will be compensated individually for their participation in this research study and may receive up to a total of $80 compensation. Compensation will be prorated at $20 for each two-week period which includes completion of data, the phone call and AE assessment. After completion of the study, participants will be sent their compensation in the form of gift cards.

8.4 Protection of Human Subjects Training

All research personnel will complete human participant protection training through CITI.

8.5 Potential benefits of the Proposed Research to Human Subjects and Others

Potential benefits of study participation may include improvement in sexual function, but improvement is in no way guaranteed.

8.6 Importance of Knowledge to Be Gained

Data from this study will provide critical information about how to design a well powered efficacy study that assesses the impact on sexual function and satisfaction from addressing more than one element of decreased sexual function. These data will add to

the science that will likely increase the development of other intervention studies trying to address this critical issue.

9.0 Data and Safety Monitoring

The study team will meet every six months or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations), and data completeness. These regular meetings will be documented and result in a Data and Safety Monitoring Report form that will be completed and signed by the Principal Investigator or by one of the co-investigators. These reports will be filed with the IRB during the scheduled continuing review.

10.0 Adverse Event Reporting

Oversight of the progress and safety of the trial will be provided by the PI and Co-I. This study presents minimal risk to subjects. Adverse events (AEs) are not anticipated; however, study staff will assess AEs during follow up phone calls. Any occurring AEs will be documented using the CTCAE version 5 and reported to the IRB per institutional guidelines.

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