FOX CHASE CANCER CENTER
TEMPLE HEALTH

Protocol Title

Addressing Sexual Concerns in Breast Cancer Survivors: Randomized Controlled Trial of a Novel Couple-Based Intervention

Principal Investigator

Jennifer B. Reese, PhD

Participating/Collaborating Institutions:

Temple University
Duke University Medical Center
Cancer Support Community

Statistician:

Elizabeth Handorf
Jill Hasler

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1.0 Introduction

Over half of breast cancer survivors experience sexual concerns[1-3] resulting from physical changes due to breast surgery, chemotherapy, and hormonal therapies; emotional changes; and relationship difficulties.[4-6] In contrast with many aspects of quality of life (QOL) that tend to improve over time for breast cancer survivors, sexual concerns often persist for years.[7-10] As a result, many breast cancer survivors and their partners may wish to resume a satisfying intimate relationship after treatment ends but encounter difficulties in doing so. Sexual concerns often go unaddressed,[11-13] can lead to clinically significant psychological distress,[8,14] and have a negative impact on survivors' relationships and quality of life.[2,6,15,16] Thus, addressing sexual concerns and improving sexual function is of critical importance to the long-term adjustment of these survivors.[17-20] Given the central role of the intimate relationship in breast cancer survivors' sexual experiences,[5,21] a couple-based intervention that systematically involves the partner may be the most effective approach for addressing these concerns and improving function.[14,21] Yet to date, there have been no RCTs testing the efficacy of a couple-based intervention targeting sexual function for breast cancer survivors.[22]

2.0 Objectives

The objective of the proposed study is to evaluate the IE intervention in 120 female early stage breast cancer survivors reporting sexual concerns and their intimate partners. Couples will be randomized 1:1 to receive either the IE intervention (Intimacy Enhancement; IE) or to a previously tested attention control condition (Living Healthy Together; LHT). We will evaluate IE effects on a range of patient and partner sexual, relationship, and psychological outcomes and examine treatment mediators and moderators.

2.1 Specific Aims

Specific Aim 1 (Primary Aim): To evaluate whether the IE intervention will lead to a significantly greater increase in patient sexual function from pre-treatment to post-treatment and 3- and 6-month follow-ups compared to the LHT condition.

Specific Aim 2 (Secondary Aim): To evaluate whether the IE intervention will lead to significantly greater improvements in (a) partner sexual function and (b) patient and partner relationship intimacy and quality and psychological distress from pre-treatment to post-treatment and at 3- and 6-month follow-ups, compared to the LHT condition.

Specific Aim 3 (Secondary Aim): To evaluate whether increases from pre- to post-treatment in patient sexual communication and self-efficacy for coping with sexual concerns mediate the beneficial effects of the IE intervention on patient sexual function at 3- and 6-month follow-ups.

Exploratory Aim 1: To explore whether age ($\leq$ 45 versus > 45 at diagnosis) and race/ethnicity (White versus non-White) moderate intervention effects on the primary outcome of patient sexual function.

Exploratory Aim 2: To identify participation barriers and intervention preferences of breast cancer survivors who choose not to participate in the Intimacy Enhancement study.

2.2 Research Hypotheses

Hypothesis 1: The IE intervention will lead to an increase in patient sexual function from pre-treatment to post-treatment and 3- and 6-month follow-ups compared to the LHT condition.

Hypothesis 2: The IE intervention will lead to significantly greater improvements in partner sexual function, patient and partner relationship intimacy and quality, and psychological distress from pre-treatment to post-treatment and at 3- and 6-month follow-ups, compared to the LHT condition.

Hypothesis 3: Increases from pre- to post-treatment in patient sexual communication and self-efficacy for coping with sexual concerns will mediate the beneficial effects of the IE intervention on patient sexual function at 3- and 6-month follow-ups.

3.0 Background/Rationale

Nearly one third of all new cancer diagnoses in women in 2016 were for breast cancer.[23] For the majority of women (61%) diagnosed with localized breast cancer, the 5-year survival rate is 99%.[23] Advances in detection and treatment improve survival for breast cancer, yet these life-extending treatments often come at a considerable cost for survivors' intimate relationships.[15,24] As many as 70% of breast cancer survivors report experiencing sexual concerns that impact their sexual function.[8,25] Common concerns include those that are biological (e.g., vaginal dryness, pain during sex),[21,26,27] psychological (e.g., loss of sexual desire),[28,29] or social in nature (e.g., reduced sexual activity; see Table 1).[4,5,30,31] Some of the most chronic and distressing sexual concerns for breast cancer survivors result from the estrogen suppression effects of chemotherapy and hormone therapy (e.g., aromatase inhibitors).[2,26,32] Post-surgery body changes, including the loss of breast and nipple sensitivity, can interfere with sexual activity and impede women's sexual arousal, a key component of women's sexual function.[27,28,33,34] Loss of sexual desire is one of the most common problems with sexual function for breast cancer survivors, and is among the most problematic because it can significantly disrupt women's intimate relationships.[2,15,35] Yet, although breast cancer survivors' physical and emotional health tend to improve over time after treatment completion, problems with sexual function and related concerns tend to persist and can therefore lead to long-term negative consequences for the intimate relationship, and psychological distress.[7,36-38] Further, breast cancer survivors with more severe sexual concerns report higher disease interference and worse QOL,[15] suggesting the critical importance of addressing such concerns.

In prior pilot studies in couples facing colorectal cancer, we demonstrated that a 4-session Intimacy Enhancement (IE) intervention delivered via telephone had positive effects on patient and partner sexual and relationship outcomes.[14,39-41] The couple-based IE intervention includes education and training in cognitive and behavioral skills to cope with sexual concerns. It is grounded in social cognitive theory (e.g., emphasizes self-efficacy for coping with sexual concerns)[42] and applies effective practices drawn from cognitive behavioral couple therapy[43,44] (e.g., communication skills training) and sex therapy (e.g., sensate focus).[45,46] With breast cancer survivors' input, we modified the IE intervention content to optimize relevance of the educational materials and adapt skills training and practice for this population.[14] Preliminary results from a pilot trial in breast cancer survivors and their partners suggest this intervention is feasible and acceptable in a diverse sample, and shows promise in improving patients' sexual function and related patient and partner outcomes. However, a full-scale randomized controlled trial is needed to evaluate the IE intervention's efficacy, investigate mediators of treatment effects, and explore potential intervention moderators.

4.0 Study Design

4.1 Recruitment methods

Number of subjects per year projected at FCCC	Total number of subjects at FCCC	Number of subjects nationally or internationally (if applicable	Number of subjects at collaborating institutions (if applicable)
Up to: 60	Up to: 180	0	125

The human subjects in this entire project include approximately 120 breast cancer patients and 120 spouses or partners of breast cancer patients who will be asked to provide their time and personal

information as part of the intervention study, plus an additional estimated 35 to 40 patients who will complete the developmental survey (exploratory aim 2), for a total of approximately 280 participants. Participants will be recruited primarily from FCCC/Temple and Duke University Medical Center (DUMC). DUMC will serve as a separate recruitment site from FCCC and will operate under its own IRB. DUMC study staff will be supervised by the site Principal Investigator, Dr. Laura Porter. Oversight of recruitment challenges and data collection will be done by FCCC.

Two key methods for recruitment were used successfully in our pilot trial at for site-based recruitment at FCCC and will be utilized again for the larger proposed trial. Potentially eligible candidates will be identified from each provider's clinic schedules and then the research assistant will query the provider as to the patient's eligibility. This pre-identification process involves pre-screening of patients using their medical records on major characteristics (e.g., disease stage, current treatment status, length of time since treatment, ECOG score) to reduce unnecessary burden of contacting patients who will not screen in or of contacting patients who may be ill. If the provider approves, a letter will be sent to a candidate summarizing the research study from the patient's provider including a phone number for the patient to call to indicate that she is not interested in pursuing the study further. Identification of patients may also occur through the tumor registry at FCCC, TUH, and DUMC and/or provider schedules (for patients who cannot be approached in clinic for any reason).

Temple patients will be identified either through Dr. Aruna Padmanabhan's clinic schedule or the TUH cancer registry. The TUH cancer registry will include patient MRNs, marital status, diagnosis date, stage, and race/ethnicity, and will be provided to the study team by the manager of the registry. As with Fox Chase patients, eligible TUH patients will be identified through pre-screening of the electronic medical record. Recruiting staff will ask Dr. Padmanabhan's permission to approach any eligible patients before contacting them.

Although patient data obtained through the registry are already limited based on disease type and stage, all patient records are checked prior to sending research invitation letters in case patients' medical conditions have changed, as in the case of disease recurrence or death.

In an effort to bolster recruitment and increase the diversity of the study sample, we will recruit simultaneously through our community partnership with Sista's Daughters, Inc. (SDI). Recruitment through SDI will primarily occur through attending community outreach events including workshops, cancer support groups, and health fairs. This model can be mutually beneficial in that the community members are able to obtain useful information on health and related topics, while bolstering community-based recruitment for the research project. Dr. Reese will plan special talks on relationships or sexual health in the context of cancer or other related topics, dependent on interest. Community-based recruitment efforts (i.e., eligibility screening and enrollment) will be conducted by FCCC staff, but medical eligibility will be determined by the patient's physician using a standard form.

Through our collaboration with Dr. Alexandra Zaleta at the Cancer Support Community (CSC), we have the option of recruiting through CSC events and through email blasts sent to potentially eligible participants in the CSC Cancer Experience Registry, which as of the writing of the grant application, included 4,836 women diagnosed with non-metastatic breast cancer, of whom many report impact on their sexual lives. These recruitment methods will serve as methods of identifying potential candidates for the study; screening will proceed as for other community-based individuals, as reported below. The email blast will contain an attachment of a one-page informational handout (similar to the recruitment brochure, but in a format more suited to reading as an email attachment) and a REDCap link to a survey where patients who are opting in to be contacted about the study may provide their contact information. We may also post the flyer or informational material on the CSC website, online forums or

social media sites, and other CSC communications as appropriate, and in consultation with our CSC collaborators. These methods may also be utilized by our team in conjunction with other non-profit organizations that express interest in sharing information about the study.

In addition, we will also post study recruitment brochures or other advertisements in clinic and patient areas (e.g., education and resource room), and may also advertise through FCCC social media and through existing FCCC breast cancer-related events and newsletters.

4.1.1 Patient Contact and Screening

Pre-screening of patients' charts by our recruitment team prior to patient contact helps to ensure that only potentially eligible candidates who meet initial criteria (e.g., age, breast cancer diagnosis and stage, ECOG score, English speaking status) will be contacted regarding participation in the study in order to minimize potential patient burden.

Patients recruited through community-based methods or the CSC will be identified as described above and screening will proceed as described next. For the women recruited through the email blasts to Cancer Experience Registry members, several emails may be sent to facilitate recruitment efforts. All women recruited through the CSC will be given information about the study (e.g., study letter, brochure or informational handout) and study contact information.

The initial contact for FCCC and Temple patients will be conducted with approval from the treating physician/provider and will be from the research team and/or the treating provider. For patients identified through the FCCC and TUH registries, lists of potentially eligible candidates will be approved by the patients' provider (e.g., their treating provider at FCCC or Dr. Padmanabhan at TUH) prior to sending the introductory letter and the brochure and/or flyer. TUH patients will receive the same recruitment materials as FCCC patients. Potential candidates who have not called to opt out of the study or otherwise opted out will be called by a research member to confirm their eligibility.

For interested candidates, screening will determine eligibility and will also include a discussion of study procedures, risks, benefits, and the voluntary nature of their participation, and the fact that it will not affect their medical care if they are a patient at FCCC. Screening the patient for eligibility may occur over the telephone or in person and will include assessment of age, disease status and stage, partner status and age, treatment status and length of time since completing treatment, use of hormone therapy, hearing impairment of patient and partner, current pregnancy, past history of breast or gynecological cancer, current treatment for a concurrent cancer, current participation in marital therapy, and sexual concerns. We used many similar items, including the sexual concerns screening item, in the pilot protocol 15-8007 and have had success with these screening items. Medical record review for all patients will confirm the patients' breast cancer diagnosis, stage, and treatment status, as described in the screening script (or in pre-screening). We will use separate screening scripts for women recruited through site-based versus community-based methods because for women recruited through community-based methods, we will need permission from their clinicians to review their medical records.

Patient eligibility screening will occur privately due to the sensitive nature of the questions and using methods we employed successfully in our R21-funded pilot randomized controlled trial. In order to collect valuable eligibility data about the target population that could be used to inform our development of future studies, all screening items will be administered, and the data will be recorded if patients endorse the item allowing us to keep the information obtained during the screening discussion.

If the patient is eligible and is considering participation in the study, the study team member will obtain permission from the patient to contact the patient's spouse or partner with regard to participation, as described in the Screening Script. Partners will be screened for the purpose of determining their interest in participating in this study; there are few specific eligibility criteria for the partner (see criteria in Table 1 below), which will be determined during the patient's screening. To ensure adequate understanding of the study by both members of the couple prior to consenting, a study team member will speak personally with both members of the couple in order to ascertain an adequate level of understanding by both members of the couple prior to giving them permission to consent for the study and proceed with enrolling.

The patient may prefer to speak with the spouse/partner initially herself. In this case, the recruiter may follow-up with the patient at a later time to assess continued interest and to speak with the spouse/partner to describe the study and/or gauge understanding of the study procedures. The recruiter may also email the partner with a separate recruitment email and study flyer designed to describe the study to partners. The partner flyer may also be given to the patient to share with her partner, if the patient is unwilling to provide her partner's contact information at that time. In the case of in-person recruitment, the recruiter will nevertheless ask for permission to discuss the study with the partner, although the patient screening will occur in private (unless the patient indicates a preference for having the partner present during the discussion).

Patients recruited from the community will be asked to provide a medical record release so that their medical eligibility may be confirmed with their breast cancer providers prior to enrollment. Only patients who screen in as likely eligible during the initial recruitment screening call will be asked to provide authorization for release of their medical records (See 9.1 Consent Process for Intervention Study for more information about the medical records release form). Patients who do not authorize release of their medical records in order to confirm eligibility will not be enrolled on study.

Patients who decline to participate in the intervention study will be approached to complete a developmental survey (Exploratory Aim 2) assessing their reasons for nonparticipation and potential preferences for similar interventions.

4.1.2 Participant Reimbursement

Patients and partners in the study will receive compensation in differing amounts after completion of individual surveys using amounts consistent to those used in prior couple-based intervention studies conducted by the study team: pre-treatment/baseline ($25 per person, $50 per couple); post-treatment ($25 per person, $50 per couple); 3-month follow-up ($40 per person/$80 per couple), and 6-month follow-up ($50 per person, $100 per couple). The total possible compensation is $140 per person ($280 per couple). Compensation will be provided in the form of gift cards.

Study-eligible patients who refuse the intervention study but complete brief exploratory surveys ("intervention refusers") will receive $10 for participation, also in the form of gift cards. Regardless of the method of reimbursement, a research team member will confirm receipt of the compensation and will document this in our research files.

Gift cards will be sent individually via US Mail upon receipt of the participant's survey, but may also be given in person if the patient is seen in clinic. Participants will be asked to sign a document confirming receipt of their gift card and will mail back to the study team. Once payment confirmation has been received, the study team member will document this in our research files.

4.1.3 Inclusion and Exclusion Criteria

Overall, eligible patients for this study will be adult (≥ 18 years) partnered breast cancer patients who have completed active treatment for stage T1-T4, N0-N2, M0 non-recurrent breast cancer between 6 months and 5 years prior who report sexual concerns (see Table 1). Patients' spouses or partners must also be ≥ 18 years old.

Table 1. Inclusion Criteria
• Female • Age ≥ 18 years • Has a medically confirmed diagnosis of non-recurrent breast cancer (Stages T1-T4, N0-N2, M0) • Completed active treatment (e.g., chemotherapy, radiation therapy, surgery, immunotherapy) 6 months-5 years ago (current use of endocrine therapy is acceptable) • Is currently in a partnered relationship that could involve sexual activity (as determined by eligibility screening script) • Has a partner or spouse who is ≥ 18 • Lives with a romantic partner ≥ 6 months • Score of ≥ 3 on Patient Care Monitor Sexual Concerns screening item[47]
Exclusion Criteria
• Patient or partner is not able to speak and read English, as stated in medical record, as observed by study team member or in self-report • Patient or partner ECOG Performance score > 2 OR medically unable to participate as judged by physician/in medical record or by self-report • Patient or partner has a hearing impairment • Patient and partner do not have reliable telephone access • Patient has overt cognitive dysfunction or psychiatric disturbance such as suicidal ideation or severe mental illness, as observed or judged by the researcher, physician or referring source, or self-report • Patient past or current history of any cancer other than non-melanoma skin cancer, including prior breast cancer • Patient is currently participating in couple/marital therapy • Patient is currently pregnant

Because male breast cancer patients may experience unique sexuality concerns, we will recruit only female breast cancer patients for the study patient sample. There are no exclusions based on race or ethnicity and every effort will be made to include a diverse patient sample for the current study. Patients are excluded if they are currently participating in couple or marital therapy to avoid confounding improvement in the IE intervention with improvement in co-occurring therapy. Further, we also exclude patients with past or current history of breast or other cancers, as such patients may have prior sexual complaints and have different needs. Pregnant patients are also excluded because they may have different sexual function and sexual concerns. Patients and partners with a hearing impairment are excluded due to the nature of this intervention as occurring over the telephone and therefore requiring active listening. Non-English speakers are similarly excluded. Patients who are medically unable to participate, as determined through an ECOG score, self-report, medical record, or provider, are excluded because participants are asked to engage in behavioral exercises between intervention sessions and such patients may not be able to participate fully in these study activities; similarly, if patients deem their partners medically unable the couple will be ineligible. Finally, because we are collecting outcome data on patients' psychological distress and well-being, and because cognitive dysfunction and psychiatric illness could interfere with study activities, patients with overt cognitive dysfunction and psychiatric disturbance are excluded, as described above in Table 1. No exclusions will be made for any

part of the investigation based on sexual orientation, which means that same-sex couples may participate.

Participants in Aim 2 completing the developmental surveys are patients who meet eligibility criteria for the pilot trial (Aim 2) but decline to participate in the trial. This may be because they do not have time or interest in participating in the full trial or for other reasons, and the developmental survey study allows them the opportunity to contribute to these research efforts in a different way.

4.2 Data Collection and Measures

4.2.1 Medical Data Collection

Because patient self-report about medical history can occasionally differ from the data on the same items in patients' charts (e.g., treatments received), we will collect the following data on enrolled patients through medical chart review: date of diagnosis and disease stage, dates and types of treatments and surgeries received for breast cancer, current treatment status, current medication use (including endocrine therapies), and current menopausal status. The data abstraction will be performed by study staff and entered into our de-identified databases. This medical chart review is documented in the consent form. We will also ask study candidates permission to keep the medical data (and other data) we collect during the screening process so that we may compare candidates who end up agreeing to participate in the study versus do not agree on these variables.

4.2.2 Self-Report Data Collection

An overview of study measures and collection time points for participants, including number of items in each scale, is in **Table 2**. After consenting, patients and partners will complete outcome measures at baseline, post-intervention, 3-month follow-up, and 6-month follow-up through a web portal on their home computers using REDCap.

REDCap is a secure, web-based application that is flexible enough to be used for a wide variety of research studies, offers intuitive interfaces for data entry and real time data validation, and supports easy data manipulation with audit trails and reporting capabilities, including automated export to common statistical packages. REDCap for electronic data collection is preferred over paper and pencil administration for this study because: (1) it can be completed in less time and is therefore potentially less burdensome for participants; (2) it is less burdensome to the investigators in terms of both collection and data entry – essentially eliminating the need for by-hand data entry of self-report measures; (3) it leads to fewer human errors because it obviates the need for by-hand data entry. Participants without computer or internet access will be able to complete data collection through US Mail using paper and pencil versions of the electronic data forms, sent to the couple by a study team member. If sent through US Mail, surveys will be sent (along with consent forms, if necessary) in separate envelopes with instructions to complete these independently from one another.

4.2.3 Self Report Measures

4.2.3.1 Primary Outcome Measure (Primary Aim)

Patient Sexual Function. Patients will complete the primary outcome measure, i.e., the 19-item Female Sexual Function Index (FSFI),[48] at all four time points (T1-T4). The FSFI is a widely used sexual function measure with established validity in breast cancer.[49,50] The FSFI is an optimal primary outcome measure because it is comprehensive and multi-dimensional, in that it assesses biological, psychological, and social dimensions of women's sexual experiences including desire, arousal, pain, and satisfaction with sexual relationship, all of which may change due to participation in the IE intervention.[17,51,52] Further, in our breast cancer pilot trial, we found a very large effect size for patient sexual function (Cohen's d=1.30).[53] The total score will be used as the primary endpoint as it reflects women's overall sexual

function. In addition, we will conduct separate models for each sexual function domain as a supplemental analysis to clarify which domains of sexual function may be driving any effects on overall function. FSFI scores are sensitive to increases in response to participation in behavioral (non-medical) intervention trials in women with cancer up to the proposed 6-month time point.[17,54]

4.2.3.2 Secondary Outcome Measures (Aim 2)

Partner Sexual Function. Partners will complete either the IIEF (if male)[55] or the FSFI (if female). Like the FSFI, the IIEF is a premier comprehensive sexual function measure with significant research in cancer populations,[51,56,57] assessing multiple domains of function including desire, arousal, and satisfaction.[56] Total scores will be used. Patient Sexual Distress. Patients will complete the 13-item validated Female Sexual Distress Scale-Revised (FSDS-R)[58]. The FSDS-R assesses the degree of distress and dissatisfaction related to a woman's sex life over the past 30 days, and has been used successfully in both observational and intervention studies with breast cancer survivors.[8,10,59] Relationship Intimacy. The Miller Social Intimacy Scale (MSIS)[60] is a 17-item scale assessing emotional intimacy, closeness and trust toward an individual's partner used in prior couple-based studies by our team,[61] which was sensitive to increases in our pilot IE studies.[39,40] Relationship Quality. The 7-item Dyadic Adjustment Scale (DAS-7)[62] is an abbreviated form of the DAS that focuses on consensus in the relationship and correlates well with the full DAS.[63] The DAS-7 distinguishes between distressed and non-distressed couples,[64,65] is sensitive to change in response to couples' interventions,[66,67] and shows excellent construct validity in breast cancer.[38,68,69] Psychological distress will be assessed through depressive symptom and anxiety scales (PHQ-9 and GAD-7, respectively),[70,71] which are validated and widely used in cancer and medical populations.[72]

4.2.3.3 Mediators (Aim 3)

Patient and Partner Sexual Communication. Sexual communication is assessed through a brief 6-item version of the Dyadic Sexual Communication Scale (DSCS).[73] The DSCS assesses the quality of communication in a couple's intimate relationship specifically related to sex that has been used successfully in cancer studies.[40,74] The original scale has 13 items. However, with the aim of reducing participant burden we conducted several analyses including item response curves and correlational analyses to determine whether a shorter version of the DSCS would be valid without losing information. These analyses suggested items 2, 3, 4, 10, 11, and 12 provided 95% correlation with the larger scale. Thus we will use these items in place of the larger scale. Patient and Partner Self-Efficacy for Coping with Sexual Concerns. Self-efficacy for coping with sexual concerns is assessed through three items measuring participants' confidence in their ability to deal effectively with sexual concerns, communicate effectively about sexual concerns, and enjoy sexual intimacy despite physical limitations. These items were developed using standard methods for constructing self-efficacy scales according to social cognitive theory[75] for the IE colorectal cancer study and have high internal consistency as a single scale (Cronbach's alpha=.91).[39,40] Items use a 0-10 rating scale and reference the past week.

4.2.3.4 Moderators (Exploratory Aim), Covariates and Other Measures.

The moderators of patient age and race/ethnicity will be assessed using medical records and pre-treatment self-report survey, respectively. Covariates. Other socio-demographic characteristics (i.e., education, sexual orientation, marital and work status, income, relationship length) will be assessed through self-report. Medical comorbidity for patients and partners will be obtained by a validated self-report comorbidity measure (Self-Administered Comorbidity Questionnaire, SCQ)[76]. In order to reduce participant burden and prevent distress, we have modified this measure for patient participants by removing the item asking whether the participant has cancer. We will keep this item for partner participants. Clinical patient characteristics (e.g. menopausal status, comorbidity, types of treatments) will be obtained through medical chart review. Other Measures. We will collect data on frequency of patient sexual activities and use of sexual aids assessed with items from the PROMIS Sexual Function

measure.[77,78] We also include two items that we developed and assessed in a prior prospective study in colorectal cancer that assess the extent to which sexuality is important to the individual, based on a theoretical model of flexible coping developed by the PI.[79] We are also including the SexFlex Scale, which is a 6-item scale measuring sexual script flexibility when coping with sexual problems.[80] To assess intervention acceptability, at post-treatment (T2), all participants will complete the CSQ-8[81] and additional questions assessing ease and helpfulness of participation and therapeutic rapport.[40] Based on Borkovec's research,[82] an intervention credibility measure ("Program Evaluation Form") will be completed after session 1 and again at the post-intervention assessment. All participants will complete surveys after session 1, 2, and 3, and again at the post-intervention survey assessing engagement with the material between sessions ("Materials Review Form"). Lastly, we have included a Coronavirus Impact Scale at baseline and six month follow-up to assess the effects the coronavirus pandemic has had on couples' lives, including their relationship and intimacy.

4.4.3 Developmental Self-Report Survey Data (Exploratory Aim 2)

All data collected from participants in Exploratory Aim 2 (developmental survey study) will be collected using the Developmental Survey, which will be administered verbally using a standardized interview format. This verbal survey collects information on patients' reasons for lack of interest in participating, preferences for resources or programs addressing sexual/intimacy concerns, relationship length/quality, level of confidence in coping with sexual concerns, and race/ethnicity. In addition, if patients endorse the item from the screening script with regard to keeping their information from the screening, we will enter these information (e.g., age, breast cancer data) into our de-identified research files for further descriptive information about this sub-sample.

Table 2. Outcome Measures										
Measure	**Construct**	**# Items**	**Baseline**	**Session 1**	**Session 2**	**Session 3**	**Session 4**	**Post-Treatment**	**3-Month Follow-Up**	**6-Month Follow-Up**
Primary Outcome										
Female Sexual Function Index (FSFI)*[48]	Patient Sexual Function	19	X					X	X	X
Secondary Outcomes										
Female Sexual Function Index (FSFI)[48] International Index of Erectile Function (IIEF)[55]	Partner Sexual Function	19/15	X					X	X	X
Female Sexual Distress Scale-Revised (FSDS-R)*	Sexual distress	13	X					X	X	X
Miller Social Intimacy Scale (MSIS)[83]	Relationship Intimacy	17	X					X	X	X
Dyadic Adjustment Scale-7 item (DAS-7)	Relationship Quality	7	X					X	X	X
Patient Health Questionnaire-9 item (PHQ-9)[70]	Distress (depression)	9	X					X	X	X
Generalized Anxiety Disorder 7-item (GAD-7)[71]	Distress (anxiety)	7	X					X	X	X
Mediators										
Dyadic Sexual Communication Scale (DSCS)[84]	Sexual Communication	6	X					X		
Beliefs (self-efficacy)[75]	Self-Efficacy	7	X					X		
Additional Measures										
Demographic information for patient/partner	Demographic data	13/9	X							
Follow-up demographic/medical questions*	Changes to marital status/ medical history	2							X	X
Self-Administered Comorbidity Questionnaire (SCQ)[76]	Medical comorbidity	14/15	X							

Sexual Self-View	Importance of Sexuality to Self	2 BL/ 1 FU	X					X	X	X
SexFlex Scale[80]	Sexual Script Flexibility	6	X					X		
PROMIS Intimate Activities/Use of Sexual Aids*	Intimate Activities & Use of Sexual Aids	8	X					X	X	X
Program Evaluation Form	Intervention Credibility	3		X				X		
Materials Review Form	Intervention Adherence	4		X	X	X		X		
CSQ-8[85]	Intervention Acceptability	8						X		
Additional Acceptability Questions[40]	Intervention Acceptability	14						X		
Skills Assessment**	Utilization of Skills	5						X	X	X
Coronavirus Impact Scale	Impact of Coronavirus Pandemic	19	X							X
Total # of items in baseline *Patients* *Partners*	 *147* *119*									
Total # of items in post-treatment survey *Patients* *Partners*	 *134* *109*									
Total # of items in 3- month survey *Patients* *Partners*	 *88* *61*									
Total # of items in 6-month survey *Patients* *Partners*	 *107* *80*									

* indicates that only patients complete the measure; **indicates that only IE participants complete the measure

4.3 Overview of Randomization and Intervention Conditions

Couples will be randomized with an allocation ratio of 1:1 to either the IE or the Educational Control (Living Healthy Together) condition with stratification by age at diagnosis ($\leq$ 45 vs. > 45) using the age obtained from the medical record (or by the patient during screening, if age at diagnosis is not available in the medical record). The statistician (Dr. Handorf) will generate the randomization sequences using an automated randomization procedure in REDCap that limits prediction of allocation and protects masking of allocations. Randomization in blocks of four will guarantee that after every four assignments the study arms will have equal numbers. Separate randomization tables will be used for FCCC, Duke, and community participants to minimize the potential for unequal randomization by site.

Randomization will occur once both members of the couple have consented, completed baseline surveys, and are scheduled for their first intervention session. Randomization will occur centrally at the primary site by a staff member uninvolved in recruitment (to reduce the potential for bias in randomizing participants onto certain conditions). Once randomized, the couple will be sent sealed study materials along with the instructions to leave the envelopes sealed until they "meet" with their interventionist for session 1. It is important to keep the study condition a secret from participants until Session 1 to reduce the chances for unequal drop-out prior to Session 1, which could occur if patients/partners are more motivated to attend sessions in one study group as opposed to the other.

4.3.1 Interventionists

All sessions will be conducted with the couple by trained interventionists with a Masters or doctoral degree in psychology or clinical social work and certified competent in the interventions by the PI. As established in our pilot trial, interventionist training consists of (a) background readings on key topics including breast cancer stages and treatments, common sexual and non-sexual side effects (e.g., stress, fatigue),[86,87] sexual response,[88] key techniques such as cognitive behavioral couple therapy[43] and sensate focus therapy,[89] theoretical models,[79,90] and cultural issues in couple and sex therapy;[91,92] (b) an in-person workshop or web conference which includes review of readings, protocols, and specific skills (e.g., communication skills training), role plays, and discussions, (c) listening to a tape of a well-executed case for each condition, and (d) complete IE and LHT test cases using intervention materials. During the trial, Dr. Reese and/or Dr. Porter will hold regular supervision sessions among the interventionists to ensure adequate quality of the delivered interventions. Interventionists will take standardized clinical notes on their sessions not containing identifying participant information and these notes will be discussed during supervision sessions. All supervision sessions are confidential; no identifiable information about participants is retained in clinical notes or supervision records. The quality assurance procedures regarding the delivery of the intervention are described further in section 16.0.

4.3.2 Intervention Format

All sessions will be delivered over the telephone. In our prior work, participants found the telephone-based format desirable for addressing the intimate topic of sexuality and many preferred it over face-to-face.[40] This format is also well-suited to reach post-treatment and long-term breast cancer survivors, who report the greatest interest in obtaining help for their sexual concerns,[16] and to whom eligibility for this study is limited. Audio calls will be made using cell phone, landline service, or an online telecommunication application, if necessary (e.g., Skype) to the couple's preferred mobile or landline using speakerphone. All sessions will be recorded by the interventionist, and these audio recordings destroyed when the study is completed. The study consent form informs participants that their sessions will be audio recorded and participants are instructed not to sign the informed consent form if they do not agree to audio recording.

Intimacy Enhancement (IE) Intervention. The proposed IE intervention content is outlined in **Table 3**[93,94] and includes four structured sessions. A couple-based intervention is ideal for breast cancer survivors because most survivors want to address their sexual concerns in a couple-based format[14] and because couple-based interventions are more effective at improving sexual outcomes in this population.[95,96] The first session is intended to be longer (approximately 75 minutes) because of the nature of the first session as involving rapport-building, information gathering, and providing education. Subsequent sessions will last approximately 60 minutes.

The IE protocol includes techniques adopted from sex therapy, including sensate focus (non-demand sensual touching exercises, usually with an "intercourse prohibition" to reduce performance pressure),[45] and cognitive behavioral couple therapy (e.g., goal-setting, communication skills, cognitive restructuring, engaging in activities to build intimacy).[43] Content also integrates a model of coping with sexual concerns developed by the PI that emphasizes flexibility in thoughts and behaviors, and encourages more inclusive thinking about how sex and intimacy are enacted within the relationship.[79,97]

Participant handouts will reinforce educational topics, provide opportunities for interactive exercises, or otherwise reinforce skills learned during the sessions. Weekly home behavioral skills practice are reviewed at the beginning of each session, including proceeding through a stepped set of sensate focus exercises with the goal of reducing avoidance of sensual behaviors and increasing intimacy.

Table 3. Proposed content of IE Intervention

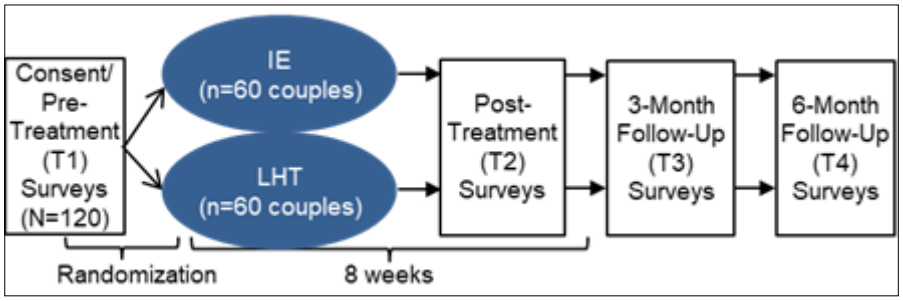
Session	Topic	Education Topics	Skills	Home practice

1 (75 min)	Introduction to Intimacy Enhancement	1. Models of female sexual function 2. Effects of BC on sex and intimacy 3. Identify and normalize problems 4. Introduce sensate focus	1. Goal-setting 2. Behavioral physical intimacy coping 3. Coping with sexual difficulties	1. Read educational material 2. Sensate focus
2 (60 min)	Improving Intimacy through Communication	1. Effective communication 2. Communicating about intimacy 3. Feedback on in vivo practice	1. Communication 2. Behavioral physical intimacy coping	1. Communication practice 2. Sensate focus
3 (60 min)	Improving Intimacy through Thinking and Doing	1. Impact of BC on body image 2. Using problem-solving vs acceptance 3. Current physical/medical treatments 4. Model of cognitions and intimacy 5. Broadening range of intimate activities	1. Identify/restructure inflexible thoughts 2. Emotional intimacy through engagement in activities 3. Coping with sexual difficulties 4. Behavioral physical intimacy coping	1. Novel intimate activity 2. Sensate focus
4 (60 min)	Planning Ahead for Intimacy	1. Review of skills and education 2. Evaluate progress toward goals 3. Plan for continued skill practice 4. Anticipate/ plan for challenges	1. Goal-setting 2. Behavioral physical intimacy coping	None

Living Healthy Together Intervention. The Living Healthy Together (LHT) intervention focuses on delivering education and support across a range of topics relevant to women with breast cancer. Research has found that social support, sleep and fatigue, and stress, and diet and nutrition are among the top concerns for breast cancer survivors.[98,99] Moreover, many of these concerns also affect women's sexual function.[100] We learned during the administration of these sessions in our prior trial that many of these concerns, and the patient's cancer experience, can also affect the partner, such as by impacting the partner's sleep or eating habits. The LHT intervention demonstrated very good credibility and acceptability in our pilot study. Importantly, participants in this condition rated the intervention highly in terms of therapist rapport and skill. Notably, there was no attrition from this condition, further supporting the notion that this condition was acceptable to participants. However, a review of participants' survey responses as well as of the discussions during clinical sessions suggested that the LHT condition could have been more engaging with participants, such as by including behavioral skills practice as for stress management techniques. Thus, we plan to enhance the LHT condition by including a longer time to work on stress management, and to include behavioral practice of stress management techniques in these sessions. In short, this condition includes education on finding support and the breast cancer experience (Session 1), fatigue and sleep (session 2), stress and stress management (Session 3), and diet and physical activity (Session 4). LHT couples will be encouraged to engage with the material between sessions by completing readings, trying out strategies, and seeking out resources and information.

4.4 Time Commitment for Participants and Study Schema

On average, we anticipate that participants will take about 6-8 months to complete the study from consent to post-treatment assessment. Baseline and follow-up surveys will take approximately 30 minutes to complete. We expect that consent will occur no more than 2 weeks prior to the initiation of the first intervention session, although participants can begin participation in the intervention as soon as both members of the couple complete the baseline survey. The intervention sessions are intended to be delivered at weekly intervals. However, realizing that patient and partner health or other circumstances may arise that can delay sessions, we will consider completion of all four sessions within 12 weeks of randomization to be within protocol. Completion of the post-treatment survey by both members of the couple should occur 2-7 days after completing the last intervention. Couples will receive the final two surveys 3 and 6 months after completing the last intervention session and will be asked to complete these surveys within 2



weeks. Thus, the minimum study duration would be approximately 7 months, and the maximum study duration would be approximately 9 months. This protocol will allow for skipped survey assessments, meaning if a participant does not return his or her survey within the 2 weeks outlined above, they will not be withdrawn from the study and will be permitted to complete the remaining study surveys.

4.5 Efforts to Improve Retention to Follow-Up Assessments

To improve retention of study participants through the longer term follow-up (i.e., 3- and 6-month), we will send couples letters in advance of the final two surveys thanking the couples for their participation to that point and letting them know that they will soon receive links to the upcoming (3 or 6 month) study survey. The reminder letters may be accompanied by a small study-related token for the couple (e.g., Coping Together After Breast Cancer-branded pens).

4.6 Developmental Survey (Exploratory Aim 2) Procedures

Eligible patients who refuse the pilot trial will be given the opportunity to participate in the research (Aim 2) by engaging in a brief telephone survey (or in-person, depending on the method of recruitment) assessing their reasons for not participating and preferences for interventions addressing sexual concerns. In addition, we will use the data obtained during screening so that this subgroup of patients may be compared with the women who agreed to participate in the trial.

The administration of this survey will likely occur at the time of screening but may occur up to one month later if necessary. This survey will be administered only once and contains 12 items. Questions assess patients' reasons for non-participation in the intervention study, about intervention preferences, and about preferences for resources, as well as two questions on race/ethnicity.

If administered in clinic, patients will be asked the survey questions privately; if necessary, partners will be asked to leave the room to ensure patient privacy. If the patient does not want to be interviewed alone in the clinic context, we will not proceed.

The time commitment for participants in Exploratory Aim 2 is approximately 10 minutes.

5.0 Risks to Participants

The major risks for study subjects are (1) discomfort at answering study questions on surveys or during intervention sessions and (2) loss of privacy or confidentiality. Due to the protections we will have in place, and based on our previous experience with couple-based interventions in which few if any such risks occurred, we believe these risks to be minimal.

We are concerned with ensuring that study questions pertaining to sexuality are handled in a sensitive manner. We have chosen standardized sexuality assessment tools that have been widely used and validated to every extent possible, and have made every attempt to ensure that the sexuality items used in the current study are minimally intrusive and appropriate. If patients do not want to answer the screening question assessing their degree of sexual concerns or discuss this topic further, they may choose not to answer this question and not to participate in the study. They will also be informed as to the nature of the items in the study that will be asked of them, and will be assured in the consent forms that they do not have to answer any questions that make them uncomfortable. We will make it clear that whether or not they answer the screening items or agree to participate in the research study will not affect their care.

6.0 Potential Benefits to Participants

We hope that participants will receive some benefit through participating in the study. However, they may receive no benefit. It is possible that the Intimacy Enhancement intervention may address patients'

sexual concerns and therefore have a beneficial effect on patient sexual function and on other patient and partner sexual, relationship, and psychosocial outcomes. All couples in the study will receive high quality information about breast cancer, as well as devoted time as a couple with a skilled counselor, and may experience benefit from this. The findings from this study will help us identify whether either or both of these interventions are helpful in improving sexual, relationship, or psychological outcomes for breast cancer patients and their intimate partners. If we find that one or more of these interventions are helpful, this could be used to help breast cancer survivors cope with the effects of their breast cancer and enhance adjustment during the survivorship period. The minimal risks to subjects are reasonable in relation to potential benefit in improving the health and quality of life of women with breast cancer.

The potential benefit of this study to knowledge and science is also significant. For breast cancer survivors who are partnered, their intimate relationships are their primary source of support. Enhancing this relationship can help breast cancer survivors adjust to changes due to their cancer treatment and improve the quality of their life. If either the Intimacy Enhancement or the Living Healthy Together intervention is found to be effective, this could have significant implications for breast cancer survivors and their partners by offering evidence-based solutions for sexual problems that result from breast cancer treatments. Given that few evidence-based programs are available, particularly those tested in couples, the value of the information gained will be significant. This program of research will help address the problematic, undertreated area of sexual quality of life. The minimal risks to subjects are reasonable in relation to the importance of knowledge to be gained on this understudied area of research and patient care.

Findings from the developmental aim may inform future research on interventions that may be well-suited to addressing the sexual concerns of a larger number of breast cancer survivors.

7.0 Provisions to Maintain the Confidentiality of Data

In order to minimize the risks associated with discomfort in answering questions, participants will be told that they do not have to answer any research questions and that, if they change their mind about participating, they can stop at any time. All information collected for this study will be kept confidential. Subjects will be told that all information will be kept in strict confidence. All patient discussions about the study and training sessions will occur in private areas or over the telephone.

In order to minimize the risks associated with loss of confidentiality, all patient data (including audio recordings of intervention sessions) will be kept confidential and secure, and all outcome data will be de-identified for analytic purposes, and none of the patients' information will be released to their physician, health care organization, or any other third party without the patient's permission, except as required by law. All computer files with patient or provider data will be password protected with access restricted to study investigators, and all data forms will be kept in locked cabinets. The file that links subject names to identifying numbers will not be kept with the data, and will not leave the institution. We will use REDCap to capture patient/partner outcome data, which is a secure, web-based application that supports easy data manipulation with audit trails and reporting capabilities, including automated export to SPSS (which we will use to maintain outcome data, in a de-identified data set), which we will use. Data that are exported to SPSS are de-identified. REDCap was developed around HIPAA-Security guidelines, and all web-based information transmissions are encrypted. All data will be stored on a server maintained by the FCCC Information Systems and Technology Department in a secure data center. The server is backed up to tape on a daily basis and is protected from inappropriate outside access by commercial grade firewalls.

All audio recordings of intervention sessions will be destroyed when the study is complete. REDCap data storage is HIPAA-compliant with efforts to keep patient data confidential; data that are exported from REDCap for analytic purposes are de-identified prior to export.

8.0 Costs to Participants

There are no costs to participants for their participation in the study.

9.0 Consent Process

9.1 Consent Process for Intervention Study

If a patient consents to participate, she is consenting to completing survey data online about their physical, sexual, and emotional health, to allow us to obtain limited medical data from her medical records, and to participating in telephone sessions with their partners that either address intimacy concerns or that deal with healthy living topics, as well as completing surveys about their participation in the interventions. Patients who are recruited from community sites will be asked to sign a medical record release so that clinical data can be collected from their breast cancer providers. Partners who participate are agreeing to everything other than the medical chart review.

First, the recruiting study team member will engage in a discussion with candidates (both patients and partners) with respect to the study procedures, risks, and benefits. This will generally occur during the screening process. Once candidates indicate their intent to participate and an adequate understanding of the study procedures, as judged by the recruiter, the recruiter will give them instructions regarding how to consent using the web-based consent process and for completing the consent and surveys. They will be given the chance to ask questions during these verbal conversations, as well as the PI's information should they require it before moving to the next step in this process.

Next, as mentioned above, patients and partners will be sent a link (one for patients, one for partners), which they will use at home in order to complete the consent process. Completion of the consent is necessary prior to having access to the online survey. The consent form also contains a question in which the participant can indicate that he or she is willing or not willing to be contacted directly about similar studies in the future. It is clear in the form that the participant can participate in the current study regardless of his/her response to this item. Couples from TUH and the community (e.g., Cancer Support Community, Sista's Daughters) will follow the same consent process as couples from FCCC.

If patients and/or partners are unable to complete the consent process online, they will be given the option to complete a written consent form either through US Mail or in person. If necessary, we will send self-addressed stamped return envelopes for the return of these consents along with paper and pencil surveys (if necessary), and will return signed copies to the couple.

In order to reduce the likelihood that web-based survey completion will lead to attrition, as can occur when the consent process takes place outside of an in-person clinic situation, the study team will engage in several reminder calls to the patient and/or partner to assist with completion (approximately 3 but no more than 6). These may include phone calls by the PI or recruiter, and email reminders, as well as attempting to set up an "appointment" with the patient and/or partner for consent and survey completion. Once the reminders have reached the maximum, we will cease to contact the patient or partner about the study and will note this in our files.

Once both members of the couple have completed consent, the couple is considered to be enrolled. If only one member of the couple completes consent and the other decides not to participate, this couple is not enrolled because only couples can participate in this intervention study. Individuals who consent to the study (through online web-based consent or paper consent through US Mail) will be sent a

photocopy of their consent form via US Mail and will be instructed to retain this consent form for their records.

9.2 Consent Process for Developmental Survey

The process for obtaining consent for the developmental survey sub-study was implemented successfully in our pilot R21-funded trial that concluded last year. After screening and refusal of the intervention trial, as documented on the patient screening script, using a brief IRB-approved oral consent process by a recruiter/research coordinator, the participant will be given information about the voluntary nature of the study, their ability to stop at any time, and study risks and benefits. This oral consent script will also ask permission to retain the patient's data from eligibility screening for comparison analyses with intervention study acceptors.

For the following reasons, we have submitted a Request for Waiver of Documentation of Informed Consent form 45 CFR 46.117(c)(1)(2): 1) The research is not subject to FDA regulations; 2) the research involves no more than minimal risk or harm to participants; and 3) the research involves no procedures for which written consent is normally required outside of a research setting.

Patients who agree to this brief study will be given a written print-out of the written oral consent document (distinguished from the oral consent script), either in person, if they are recruited in person, or they will be sent this through US Mail if they have been recruited over the telephone. Oral consent will be obtained irrespective of the method of recruiting. The person obtaining the consent shall sign and date the consent script as a record that the oral consent discussion occurred.

10.0 Off-Study Criteria

Any participant may leave the study at any time due to distress or other reasons. We do not have a priori reasons for letting participants off the study. An exception would be if a patient or partner experiences significant psychological or marital distress during the study such that it is deemed detrimental for them to continue in our study at the expense of receiving psychological or mental health services. If this happens, we will follow the procedures listed below for Adverse Event reporting, and will recommend that the couple not continue in this study but rather receive appropriate referrals, as described below in section 15.0. We will track such events, as described below, and we expect them to be extremely rare.

In the case of attrition after randomization to either intervention, both partners may be asked if they would be willing to remain in the study for data collection only. In this case, we will attempt to obtain data from these couples at all of the pre-set time points as though they had participated in the assigned intervention at the intended time point. Because both partners must attend sessions together, if one partner wishes to discontinue telephone sessions, both partners will be withdrawn from sessions and offered the opportunity to complete the remaining study surveys. If one partner is unwilling to continue to complete surveys, we will attempt to collect data from the other partner.

If a patient's disease recurs and/or the patient needs to start active treatment during the study, she will be allowed to remain on the study and complete study activities (e.g., sessions, data collection) as usual, if she chooses, and this information will be tracked in her research files pertaining to their medical records. Because the duration of the study involvement is relatively brief, we expect these circumstances to be infrequent.

11.0 Drugs and Devices

Not applicable.

12.0 Multi-Site Research Study

As the coordinating site for this trial, FCCC staff will oversee study procedures at other participating institutions (DUMC and Cancer Support Community). This oversight includes preparation of IRB submissions, staff and interventionist training, quality assurance procedures, and regulatory adherence. FCCC staff will have access to de-identified data for participants from outside institutions in order to complete data accuracy checks. A record of participating institutions' IRB approval documents will be kept at FCCC.

The PI, who is at FCCC, will take responsibility for monitoring the safety of all phases of the research study and for ensuring that the study protocol is being enacted at all study sites.

There will be regular study team meetings, which will be concerned with discussing study progress including recruitment progress, successes and challenges in the delivery of intervention sessions, and any other issues related to the conduct of the study. These meetings will serve a key function in identifying problems or new information that arises during the study (e.g., increased distress during administration of a particular intervention condition) that could necessitate changes that need to be made to the IRB protocol or other study documents (e.g., consent form, recruitment materials). However, the PI will also encourage study team members aware of any information that could be important for study procedures to contact her as needed to disseminate this information and ensure that issues are responded to in a timely fashion.

No changes will be made to any of these documents without the approval of the PI. The PI will initiate such changes, ensure that changes are clearly documented and distributed to the study site PI's, who will then communicate that these changes have been made and implemented, and approved by the FCCC and DUMC IRB's. Any results that could impact the study procedures will be communicated to the PI if she is not aware and if changes need to be made in response to this, the PI will decide how to proceed and disseminate changes to the appropriate members of the study team.

13.0 Statistical Analysis

13.1 Overview of Statistical Analyses

Prior to conducting the primary or secondary analyses, descriptive statistics (i.e., frequencies, measures of central tendency) will characterize the sample in terms of important socio-demographic and clinical characteristics (e.g., age, education, race/ethnicity, and menopausal status) and any other relevant covariates. All outcome variables will be assessed for normality and, if necessary, normalizing transformations may be applied or change scores may be used for outcome measures in analyses. We will describe the interrelationships between all outcomes (primary and secondary) by calculating correlations. To determine whether the enrolled sample differs from eligible study refusers, we will compare these groups on key socio-demographic and clinical factors obtained during screening (e.g., age, treatments) and on severity of sexual concerns using two-sample t-tests or Chi-square tests. Any variables with significant imbalance will be entered in our between groups analyses as covariates. Study completers will also be compared to non-completers on these variables. Every effort will be made to minimize couple drop-out, although some degree of attrition is expected. Logistic regression will be used to understand what factors are predictive of drop-out at the participant level. Factors for possible inclusion in this model include intervention arm, age, level of pre-treatment patient sexual function, and interactions involving intervention arm. Reasons for drop-out will be queried, categorized, and compared within each intervention arm. Our main analyses will account for missing data using multiple imputation with chained equations (MICE).[101-103] This method will provide valid inferences provided that the probability of having missing data (i.e. drop-out) only depends on the observed data (e.g. treatment arm, baseline sexual function). We chose MICE because it can be used with multi-level models, and it has the ability to readily accommodate categorical variables.

13.2 Statistical Analyses for Aim 1 (Primary Aim; Effects of IE Intervention on Patient Sexual Function)

The primary analysis will examine whether, relative to the LHT condition, the IE condition leads to greater increases in the primary outcome of patient sexual function at all three post-treatment assessments (T2-4; post-treatment; 3-month FU; 6-month FU). We will also examine specific domains of sexual function (satisfaction, desire, arousal, lubrication, orgasm, pain) separately. In a mixed effects regression model, study condition will serve as the independent variable and patient sexual function at each time point will serve as the dependent variable; pre-treatment sexual function will be included in the model as a covariate with time included as a categorical covariate. Intervention by time interaction effects will be included to test the intervention effect at each follow-up time. Subject-specific random intercepts will account for within-subject variability. Intervention effects on patient sexual function at each follow-up are tested using F tests of combined main and interaction effects.

13.3 Statistical Analyses for Aim 2a (Secondary; Effects of IE Intervention on Partner Sexual Function)

To assess effects of the IE intervention on partner sexual function, which will generally be completed using a male-specific scale (because nearly all partners are expected to be male), we will conduct mixed effects regression analyses (as in Aim 1). Potential same-sex partner sexual function data will be handled in two ways: first, male sexual function as an outcome will be analyzed within the subset of male partners, and second, in exploratory analyses, if possible, we will use clinical cut-off scores across the sexual function scales and using logistic regression models where dysfunctional versus functional status is used as the endpoint,[104,105] controlling for the effect of partner gender.

13.4 Statistical Analyses for Aim 2b (Secondary; Effects of IE Intervention on Patient and Partner Relationship and Psychosocial Outcomes)

The outcomes in Aim 2b (relationship intimacy and quality, and psychological distress assessed through depressive and anxiety symptom scales) will be assessed using identical measures in both patients and partners. Multilevel modeling (MLM)[106] will be used to test for differences in outcomes between the IE and LHT groups over time. In our primary analysis time, treatment, and role (i.e., patient versus partner) will be treated as categorical with F-tests used to assess mean differences in outcomes. These models include all main effects and interactions among these variables. Models also include random intercepts for patients and partners, as well as the correlation between the intercepts (i.e., if a patient is high in average distress across time, is the partner also high?). Models will include a time-specific correlation between the partners' residuals (i.e., if a patient is distressed at a particular time point, is the partner also distressed at that time?). In addition to modeling the interdependence between patients and partners, MLM has the advantage of not deleting participants with missing data at some time points, thus utilizing all available data.

13.5 Statistical Analyses for Aim 3 (Secondary; Mediators of IE Effects on Patient Sexual Function)

To evaluate whether changes in either sexual communication and/or in self-efficacy for coping with sexual concerns mediate treatment effects on sexual function for patients in the IE condition at 3- and 6-month follow-up, we will use the causal inference framework for mediation described by VanderWeele and others[107-109] to evaluate whether change (increase) in the mediator variable from pre-treatment to post-treatment mediates improvement (increase) in patient sexual function. Initial models will look for mediation at 3-month follow-up; if evidence of mediation is found, we will also test mediation models which include 6-month follow-up. Effects will be estimated via structural equation modeling, and covariates (age, race, etc.) will be included to account for possible mediator/outcome confounding. Separate models will be fit for the two proposed mediators.

13.6 Statistical Analyses for Exploratory Aim 1 (Age and Race/Ethnicity as Intervention Moderators)

In the primary analysis described above, we will explore (but do not expect to find) interactions between intervention effects and both age ($\leq$ 45 versus > 45) and race/ethnicity (White versus non-White). Based

on pilot data, we estimate that approximately 30% and 25% of the sample will be classified as younger or non-White, respectively. Separate models will be fit for the 2 potential moderators. We will add age/race and interactions between the moderator, intervention, and time point in the regression model described in the Primary Aim. If the 3-way interaction between age/race, intervention, and follow-up time is significant, assessed via a likelihood ratio test, this will provide evidence that the treatment effect significantly differs by age or race. However, interaction effects not meeting statistical significance, but with an estimated magnitude > (.5 * main effect) will suggest sub-threshold subgroup effects that we will consider in planning next steps including tailoring the IE intervention.

13.7 Statistical Analyses for Exploratory Aim 2 (Developmental Aim with Study Refusers)

In this exploratory aim, we will gather information on barriers to participation by comparing study participants to eligible patients who declined to enroll in this study. Sample characteristics of the women who were study-eligible but declined to participate will be analyzed descriptively (using standard statistics including means, medians, standard deviations, frequencies, and percentages). Trial refusers will be asked to take a survey and responses to items on this survey will be analyzed descriptively and presented graphically as appropriate. We will also compare the study-eligible women who refused versus enrolled in the trial on demographic and clinical variables (age, disease stage, treatment status, length of time since treatment completion) obtained during screening, and sexual concerns using independent sample t-tests, Wilcoxon tests, Chi-square tests, or Fisher's exact tests, as appropriate. Women who refused and completed the survey will also be compared to those who enrolled on race/ethnicity, which is assessed during the developmental (refuser) survey. We will also compare the study-eligible women who refused the study but did not complete the survey with those who did complete the survey on the data available on these variables.

13.8 Power Calculations

Power calculations are based on Aim 1 (Primary Aim). On the patient sexual function measure, a change of 5 points would be considered clinically meaningful (scale range: 2-36, SD≈10). Based on pilot data, we anticipate that the SD of the change scores will be 8.2. Using our prior IE trials to guide attrition estimates, we estimate an attrition rate of 24% at 6-month follow-up, resulting in data available from 92 analyzable couples at 6-month follow-up. We will therefore have 82% power to detect a difference of 5 points in change scores, assuming a 2-sided test with type-I error (alpha) of 0.05. In our breast cancer pilot study, we found a between-groups difference in change scores on patient sexual function of 10.7 at post-treatment. Based on results of similar trials, we expect some attenuation of effects by 6-month follow-up.[17] This study is powered to detect a clinically meaningful change > (.5 * main effect) through the final assessment point. In sum, the study is conservatively powered to detect an effect of the IE intervention approximately half the size obtained in the pilot trial. The sample size of 120 couples (240 participants) was selected based on these calculations.

14.0 Data Safety Monitoring Plan

The PI will take responsibility for monitoring the safety of all phases of the research study. The research assistant or other study team member will report any adverse events he or she observes to their respective site PI (Dr. Reese or Porter) immediately; DUMC adverse events will also be reported to Dr. Reese within 24 hours. The study consent forms have the contact information for the study PI and the appropriate Institutional Review Board (IRB), and patients may contact her or their respective IRB at any time. The research team will keep a log tracking the number, nature, and frequency of adverse events that occur in both recruiting sites and overall. Because of the nature of the research as involving procedures without significant risk (e.g., surveys; telephone psychosocial intervention) there are unlikely to be any related adverse events. Given the minimal risk of this study, it is determined that a Data and Safety Monitoring Board is not necessary for the proposed study; this plan was approved by the NCI.

15.0 Adverse Events

Because of the nature of the research as involving procedures without significant risk (e.g., surveys; telephone psychosocial intervention sessions; telephone surveys) there are unlikely to be any serious adverse events and adverse events are likely to be rare. We have conducted similar studies in the past and found the risk to be extremely low. Possible risks include feeling uncomfortable or mildly distressed during questionnaire completion or during the intervention sessions given that discussions of the breast cancer experience or of the intimate relationship can be sensitive and provoke emotional reactions. Importantly, many couples' intervention studies have been conducted by members of the study team with no significant evidence of negative effects on the participants' individual or relationship well-being. A mild emotional reaction to discussions during the intervention by the patient or partner (e.g., tearfulness) is a very common reaction to the nature of the issues discussed during a cancer-related intervention, and would therefore not be considered an adverse event. Minor experiences of boredom, fatigue or discomfort during survey completion are also generally not considered to be adverse events. All participants are informed of the very minor risks of psychological reactions possibly associated with participating in the study during the informed consent process. Adverse events include significant distress or psychological reactions that interfere with study procedures such as intervention session or survey completion (e.g., severe untreated depression, suicidal intent, or extreme marital conflict). Suicidal ideation will be assessed by an item on the PHQ-9 ("Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?"), which is administered as part of the study surveys administered at all time points. Any response except "not at all" will be considered an adverse event given that it indicates suicidal ideation for at least several days or more, although this does not necessarily indicate that the study procedures were responsible for causing these feelings. In the case of a positive response on this item, the PI's (Reese, Porter), who are both licensed psychologists, or another trained member of the team will call the participant to assess current suicidal risk and need for services and will provide referrals to mental health services, if appropriate.

Any unexpected or adverse event that occurs during data collection or study procedures will be reported to the site Principal Investigator (Drs. Reese or Porter) within 24 hours, who is responsible for documenting all adverse events as well as reporting to the appropriate site IRB, if required. DUMC adverse events will also be reported to Dr. Reese within 24 hours. The research study team will bring any questionable adverse events to the attention of the Principle Investigator, and discussions will include colleagues or members of the IRB if it is unclear whether an event qualifies as an adverse event. For participants who are experiencing significant psychological distress reactions that warrant referrals to appropriate psychological services, the study team member or research assistant alerts the Principal Investigator, who would assess the need for further services. If appropriate, the PI or a trained member of the study team will provide the participant with a referral to appropriate services. The PI (Reese) and DUMC Site PI (Porter) are licensed psychologists able to make appropriate determinations and guide treatment decisions regarding psychological and marital distress. The study team will complete training in suicide prevention and risk assessment through the Columbia Lighthouse Protocol (https://cssrs.columbia.edu/). FCCC and DUMC counselors are available who are trained to provide psychological support services or to make specific referrals to other psychological counseling or psychiatric services in the area as needed. Moreover, participants experiencing relationship distress extreme enough that continuation in the study is contraindicated will be referred to appropriate marital or couple therapists if necessary and recommended to discontinue participation in the study, as previously described.

The research team will keep a log of the tracking the number, nature, and frequency of adverse events as part of each phase of the research plan. In accordance with FCCC guidelines, this protocol will employ the following mechanisms for adverse event reporting: 1) alert the FCCC review committees of any and all reports of adverse events; 2) inform all members of the study team of any all reports of adverse

events. All adverse events will be reviewed annually at the time of IRB continuing review. If 3 or more serious adverse events are reported, the study team will assess potential causes of the adverse events and, if events are clearly linked to study participation, discontinue the study. If there is any lack of clarity on the part of the study team with respect to proceeding in response to study safety events, the PI will contact a regulatory expert in order to determine how to proceed appropriately.

16.0 Quality Assurance Procedures and Participant Confidentiality

16.1 Overview of Quality Assurance Procedures

We have a number of features in place to ensure a high level of quality in our intervention study.

Quality Assurance Procedures for Implementation of Intervention Sessions. First, we are using a randomization procedure and a stringent control condition that equates for therapist time and attention. Second, we will assess patient and partner intervention credibility to determine whether credibility of both conditions is equivalent (see 16.2 for further explanation). Third, we are employing a manualized approach to treatment, in which all interventionists will use the manual to deliver both intervention conditions. Adherence to the manual will be assessed using the procedure described below in section 16.3. Fourth, the PI and site PI's will not be involved in any assessment procedures to ensure adequate blinding; similarly, the interventionists will advise participants explicitly not to share their responses to credibility items (Program Evaluation Form) or the Materials Review (e.g., homework completion) with the interventionists, which could bias participant reports. Interventionists must know which condition participants are receiving because they themselves deliver them (and in this way, cannot be truly blinded like with a placebo drug study). However, in the training of interventionists, we will emphasize that both conditions are likely to be perceived as helpful by participants and will refer to the conditions as "Group 1" and "Group 2" as opposed to "active condition" and "control condition", thus attempting to reduce interventionist bias in favor of the active condition. Fifth, the intervention sessions will be delivered by experienced interventionists with a Master's degree or PhD in a mental health profession who have experience in counseling, and preferably with experience in delivering manualized individual or couple-based interventions, thus ensuring a high level of experience and training in the interventionists delivering the interventions (see more detailed descriptions of the backgrounds of interventions in the Interventionists section (4.3.1). Experience in delivering manualized interventions is important because delivery of such interventions entails a fine balance between rapport-building and attending to the couples' needs and adherence to the intervention protocol. Finally, all interventionists will be trained to deliver both interventions (Intimacy Enhancement; Living Healthy Together). Interventionists will be trained by the PI and allowed to begin delivering sessions only once approved by the PI. Training will include role-plays of these sessions to ensure that the interventionists have had a chance for skills practice and feedback prior to leading sessions. Regular supervision sessions among the interventionists with the PI or Dr. Porter (or both) will be held once the interventionists have begun to lead sessions with couples and will ensure a forum for ongoing discussion of cases, solving problems or answering questions about delivery of the intervention, and to reinforce use of the intervention manuals. During supervision, the interventionists and supervisors will regularly discuss the extent to which the interventionists were able to adhere successfully to the manual through using session checklists.

Quality Assurance Procedures for Other Study Aspects. First, to promote transparency, the trial will be registered on clinicaltrials.gov and a protocol paper will be published. Second, we have designed standardized procedures for every aspect of study administration, from the candidate screening process to administration of the study conditions. Third, all outcome measures have demonstrated excellent psychometric properties and have prior research supporting their appropriateness in the study population and sensitivity to interventions. Fourth, REDCap, a secure web-based application, will be

used for data collection and for randomization, with an automated procedure that limits prediction of allocation and protects masking of allocations. Finally, to facilitate unbiased data collection and analysis the following steps are taken: 1) the data analyst will conduct outcome data analyses on data in which study condition is masked; 2) outcome data collection is completed in an automated fashion using REDCap, minimizing the need for contact with participants to collect study data; 3) if needed, manual data collection will be completed by study staff for whom the participant's assignment is masked to the extent possible. On an annual basis, adverse events will be reviewed across study conditions. During the annual review of adverse events, the presence of significant between-group differences could potentially warrant unmasking of the study conditions by the study biostatistician. As with most behavioral interventions, study interventionists, intervention supervisors (site PI's), and participants are not blind to study condition.

16.2 Intervention Credibility

Intervention credibility refers to the extent to which the intervention conditions are both perceived as by participants as credible and likely to be helpful. Participants will complete a 3-item Program Evaluation Form adapted from those used in other randomized controlled trials conducted by the PI and her colleagues to assess credibility immediately following session 1 and again at the post-intervention survey through REDCap, separately by patients and partners using online links. Data from this form will be analyzed after overall study data collection is completed to compare the credibility across the groups.

16.3 Intervention Adherence

Adherence refers to the extent to which the interventionist delivers the intervention according to the intervention manuals. This differs from unstructured psychotherapy, and allows us to have faith that the interventions we intend to deliver are, in fact, delivered by interventionists as well as being replicable in future studies. Telephone sessions will be audio-recorded. A reviewer with familiarity with the material who is not involved in the delivery of the intervention (Lepore, Temple) will listen to a random sample of 10-20% of cases and evaluate the adherence of the interventionist to the manual using the session checklists as a guide. Adherence to session checklists $\geq$85% will be considered satisfactory. In addition to the independent reviewer sessions may also be listened to by members of the study team or consultants for educational or training purposes.

16.4 Participant Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations required a signed subject authorization informing the subject of the following: The protected health information (PHI) that will be collected from patient; who will have access to that information and why; who will use or disclose that information; the rights of a research subject to revoke their authorization or use their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information prior to the revocation of subject authorization. To ensure confidentiality identifiers will be recorded and used with electronic data collected and all records will be secured in a locked location.

17.0 Participant Informed Consent

See separate Informed consent document

18.0 References

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19.0. Appendices

- Consent Forms
    - Web-based version of Consent
    - Paper version of Consent
- Surveys or Data Collection Tools
    - Self-Report Materials