



Protocol Title

Pilot Study of an Intimacy Enhancement Intervention for Couples Facing Breast Cancer

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Funding Source:

NCI 1R21CA191354

Initial Version Date: 05/01/2015

Amendment #8

Version date:
10/10/2016

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1.0 Introduction

Background: The majority of women diagnosed and treated for breast cancer survive 5 years past diagnosis, making quality of life (QOL) concerns highly salient. Sexual concerns are common and distressing for many women with breast cancer and serve as a major source of QOL impairment. Unlike other aspects of QOL that improve over time after breast cancer treatment, sexual concerns often persist and do not typically resolve without intervention. Yet these concerns are typically neglected in patients' care, leaving them underdiagnosed and undertreated. Addressing breast cancer survivors' sexual concerns can reduce distress, support their intimate relationships, and foster effective adjustment. However, existing sexual QOL interventions that address the sexual concerns of breast cancer survivors suffer from limitations in both content and format. For instance, existing sexual QOL interventions do not include current management recommendations and are not generally in a format that can be widely disseminated. A telephone-based format is a viable, effective alternative to in person counseling that would enhance the potential for dissemination and be ideal for reaching long-term survivors. Previously, the PI demonstrated that a 4-session telephone-based Intimacy Enhancement (IE) intervention improved intimacy and sexual outcomes for colorectal cancer patients and their partners.

Objective and Hypothesis: The central goal of this study is to examine the feasibility, acceptability, and preliminary efficacy of the IE intervention on patient and partner sexual QOL and relationship outcomes, and on patient psychosocial outcomes. We expect that the IE will show adequate feasibility, acceptability, and preliminary efficacy. Secondly, based on the rationale that barriers exist that limit participation in intensive sexual QOL interventions for breast cancer survivors, an innovative secondary aim will investigate the perspectives of study-eligible patient candidates who opt out of participating in the pilot trial. We expect that we will be able to identify the participation barriers and intervention preferences of breast cancer survivors with sexual concerns who opt out of the intensive trial in order to inform the development of different interventions for future study.

Specific Aims: (1) To pilot test the feasibility, acceptability, and preliminary efficacy of the Intimacy Enhancement intervention. (2) To identify participation barriers and intervention preferences of breast cancer survivors who choose not to participate in the Intimacy Enhancement pilot study.

Study Design: In Aim 1, we will randomize approximately 30 breast cancer survivors with sexual concerns to either the IE intervention or to an Educational Control condition (2:1). Feasibility will be measured through study accrual, attrition, and session completion. Acceptability will be assessed through a validated treatment satisfaction measure. Preliminary efficacy will be measured through estimating the intervention effect size on improved **patient and partner sexual QOL outcomes** (sexual function, sexual satisfaction and intimacy, sexual distress) and **relationship outcomes** (emotional intimacy, sexual communication, relationship quality), and **patient psychosocial outcomes** (body image distress, psychological distress). In Aim 2, concurrent with the intervention study, brief, structured, exploratory surveys with study-eligible candidates who choose not to participate in the pilot intervention study will be used to investigate barriers to participation and willingness to participate in alternative interventions drawn from a range of formats (e.g., website; written materials, other counselor) and sources (e.g., clinician, peer volunteer, counselor). These are referred to as "developmental surveys" in this protocol.

Significance: Addressing sexual and intimacy concerns can lead to improved relationship quality, mental health, QOL and even treatment adherence. Ultimately, this program of research will lead to the availability of a range of interventions well-equipped to address the undertreated area of sexual QOL for those with breast and potentially other cancers.

2.0 Objectives

2.1 Primary Objectives

2.1.1. Primary Objective I.

To pilot test the feasibility, acceptability, and preliminary efficacy of the Intimacy Enhancement intervention. We will randomize 30 breast cancer survivors with sexual concerns to either the newly adapted IE intervention or to an Educational Control condition (2:1). Feasibility will be measured through study accrual, attrition, and session completion. Acceptability will be assessed through a validated treatment satisfaction measure. Preliminary efficacy will be measured through estimating the intervention effect size on improved **patient and partner sexual QOL outcomes** (sexual function, sexual satisfaction, sexual distress) and **relationship outcomes** (intimacy, sexual communication, relationship quality), and **patient psychosocial outcomes** (body image distress, psychological distress). Effects of the intervention on other exploratory outcomes (e.g., patient and partner cancer-specific distress) will also be examined.

2.1.2. Primary Objective II.

To identify participation barriers and intervention preferences of breast cancer survivors who choose not to participate in the Intimacy Enhancement pilot study. Concurrent with the intervention study, brief structured, exploratory/developmental surveys with study-eligible willing candidates who choose not to participate in the pilot intervention study will be used to investigate barriers to participation and preferences for participation in alternative interventions drawn from a range of formats (e.g., website; written materials, other counselor) and sources (e.g., clinician, peer volunteer, counselor).

2.2 Secondary Objectives

2.2.1. Secondary Objective I.

None.

2.2.2. Secondary Objective II.

None.

2.3. Research Hypothesis

2.3.1. Hypothesis I.

We expect that the IE intervention will be considered feasible and acceptable.

2.3.2. Hypothesis II.

We expect that the IE intervention will show preliminary efficacy on patient and partner sexual outcomes, patient and partner relationship outcomes, and patient psychosocial outcomes.

2.3.3. Hypothesis III.

We expect to gather data from Aim 2 (developmental surveys) which will help characterize study-eligible candidates who choose not to enroll and to inform the development of future intervention studies.

3.0 Background

3.1 Scientific Background

Sexual Concerns are Common and Distressing in Breast Cancer. Breast cancer accounted for nearly one third of all cancer diagnoses in women in 2013 (29%).¹ Breast cancer makes up over 20% of all cancer survivors, greater than any other single group by cancer diagnosis.² Over 90% of breast cancer survivors have at least a 5 year expected survivorship and nearly all those with localized disease have a 5-year likelihood of surviving past diagnosis (98% overall),¹ making QOL

life concerns such as sexual function particularly salient for this group. Advances in detection and treatment improve survival for breast cancer, yet **these life-extending treatments often come at the cost of negatively impacting sexual quality of life (QOL)**.³⁻⁵ Up to 70% of breast cancer survivors report sexual difficulties.⁶ Common sexual concerns include both **physical problems (e.g., orgasmic difficulties, painful intercourse)**⁷⁻⁹ and **motivational/emotional concerns (e.g., loss of sexual interest, body image distress)**.^{10,11} For breast cancer survivors, surgical scarring can lead to body image distress¹¹ and loss of nipple sensitivity;³ hormonal therapy and chemotherapy can alter sex hormones, leading to distressing vaginal symptoms (e.g., dryness) and generalized symptoms (e.g., hot flashes);^{9,12} and radiation and/or chemotherapy side effects (e.g., weight gain)^{13,14} can interfere with sexual function and interest. Cancer treatment can also significantly impact the intimate relationship generally (e.g., by reducing time for enjoyable activities)¹⁵ and through its effects on sexual intimacy.¹² Sexual concerns are also **persistent for breast cancer survivors**, improving at a much slower rate than other domains of QOL such as pain and physical function.¹⁶⁻¹⁹ Breast cancer survivors rank sexual concerns (e.g., the ability to engage in sexual intercourse without difficulty) among their top concerns.^{20,21} Sexual problems correlate with poorer overall QOL and higher disease interference.²² In sum, for breast cancer survivors, **sexual concerns are common, distressing,^{10,23} persistent, and lead to reduced QOL.**

Sexual Concerns are Inadequately Addressed for Breast Cancer Survivors. Sexual concerns for breast cancer survivors generally do not improve on their own,²⁴ and often require intervention. Therefore, the importance of available empirically supported interventions that adequately address these concerns is critical. Despite this, **sexual concerns are among the most poorly addressed of cancer-related concerns for women with cancer.** In stark contrast to prostate cancer survivors, of whom the majority receives information about treatments on sexual function²⁵ and for whom addressing sexual function has become standard practice, the minority of women with breast cancer receive such information.^{25,26} In past work with the PROMIS Sexual Function Domain committee,²⁷ we examined patients' experiences of communication about sex with their oncology providers.²⁵ We found that **although the majority of breast cancer survivors (75%) reported that it was important to discuss sexual concerns with providers, only 33% reported ever receiving information.** Similarly low percentages (i.e., 10%,²⁸ 41%²⁹) have been reported in other studies, suggesting that sexual issues are addressed for the minority of those treated for breast cancer. For breast cancer survivors with identified sexual concerns, there are few empirically supported interventions available.³⁰⁻³² Alternatively, the widely disseminated websites and pamphlets addressing sexual issues for breast cancer survivors (e.g., American Cancer Society) have not been empirically evaluated. Thus, the **development of empirically supported interventions that are easily disseminated is critically important.**

Prior Intervention Studies Have Significant Limitations. Most interventions addressing sexual issues for women with breast cancer have (a) focused on alleviating particular side effects that can affect sexual function (e.g., vasomotor symptoms like hot flashes),³³ (b) included sexual concerns as one of many issues targeted,³⁴ thus reducing the breadth of concerns addressed, or (c) utilized formats difficult to disseminate (e.g., home visits).³⁵ Physical, emotional/motivational, and relationship factors all contribute to sexual problems and need to be dealt with in a comprehensive approach.³⁶ Limitations also exist with regard to the format of prior interventions. Only two prior intervention studies for breast cancer survivors that measured sexual outcomes have used a telephone format;^{37,38} both of these studies included sexuality as a side module rather than as the focus, neither included partners, and neither screened for sexual problems - which is important in light of an increasing focus on targeting interventions at the sub-populations with the greatest need.³⁹ Finally, recent empirically supported guidelines for improving vaginal dryness and discomfort and maintaining vaginal health through physical and behavioral strategies⁴⁰ need to be integrated in sexual QOL interventions. Yet as of now, no empirically supported interventions exist that include these strategies within the context of a couple-based approach. Thus, significant limitations to existing interventions exist that, if addressed, could have significant **implications on research and clinical care related to the sexual QOL of breast cancer survivors.**

Measure	Study 1		Study 2	
	PT	PR	PT	PR
Sexual Distress	-1.01	-0.56	.05	-.69
Sexual Function- Female	1.15	1.29	0.85	.18
Sexual Function- Male	0.22	0.61	0.58	1.75
Sexual Communication	0.82	0.68	-.30	0.97
Intimacy	0.29	0.53	-.06	0.51
Self-efficacy	--	--	0.66	0.57

3.2 Preliminary Studies

Previously, the PI conducted a small uncontrolled pilot study examining a telephone-based IE intervention in 14 couples facing colorectal cancer (9 completed; Study 1 in Table 1).⁴¹ This intervention aimed to improve patient and partner skills in coping with sexual concerns related to colorectal cancer and improve physical and emotional intimacy. Findings showed moderate to large effects for most sexual and relationship outcomes. Dr. Reese then compared the intervention to a wait list control in a randomized study in 23 couples (18 completed; Study 2 in Table 1).⁴² Findings showed strong positive effects on all outcomes for partners and on sexual function and self-efficacy for patients. Importantly, across both of these studies the **vast majority of participants (>75%) reported liking the telephone-based format**; qualitative responses indicated that this format was appreciated for both its convenience and comfort in discussing sensitive topics.

We recently conducted our first patient focus group within this population under IRB Protocol # 14-833 to gather data that will allow us to adapt the previously tested IE intervention to breast cancer, and have two more scheduled at the time of this submission. The objective of these groups is to identify preferences for content and structure which will be used to tailor the intervention to the needs of this population. We will also conduct cognitive interviews with approximately 5 additional breast cancer survivors to review the intervention materials and ensure their comprehensibility and appropriateness, and the IRB modification is currently pending approval for these cognitive interviews. We anticipate that the general content and structure of this intervention, i.e., a couple-based telephone intervention with four sessions addressing intimacy and sexual concerns, will remain as proposed. However, once we have analyzed all data obtained from the exploratory focus groups in IRB Protocol #14-833, we will use that data to finalize the content and structure of the planned intervention. We expect changes to be relatively minor. An outline of the IE intervention condition is submitted in the Appendix, although minor elements of this may change without altering the overall aims and subject matter of this intervention. We will submit substantial changes to the intervention content or format that we will make based on our qualitative data using a modification to the present IRB protocol once those data have been analyzed.

3.3 Significance of the Research Study

Sexual concerns are common, severe, distressing, and persistent for breast cancer survivors making this study highly significant. First, while persistent sexual problems lead to impaired QOL for breast cancer survivors, addressing these concerns can reduce emotional distress, support relationships, and foster effective adjustment to the disease. Given that sexual side effects of hormonal therapies are bothersome and can lead to nonadherence, identifying and addressing these negative sexual side effects could potentially improve adherence to such regimens. Therefore, this study has significant implications for improving patient outcomes and even adherence to medication regimens, making it of significant interest to clinicians who treat breast cancer survivors.

Second, the novel telephone-based format of the couple intervention enhances the potential for dissemination. While cancer patients with access to comprehensive cancer centers can benefit from the sexual health programs often available at these sites, patients who receive their care in community or rural cancer centers generally lack equivalent expertise and may therefore be unable to pursue appropriate treatment for their concerns. A telephone-based intervention could be easily disseminated to couples who are unable to attend in-person visits due to such geographical limitations, cost, or the burden of travel. Moreover, this intervention could be easily integrated into existing telephone counseling programs for cancer survivors such as CancerCare, which employs brief, structured evidence-based treatment protocols. Findings will also have implications for researchers considering telephone-based interventions for cancer survivors and their family members.⁴³ The web-based format for outcome data collection further reduces participant burden and contributes to the novelty of the study methods.

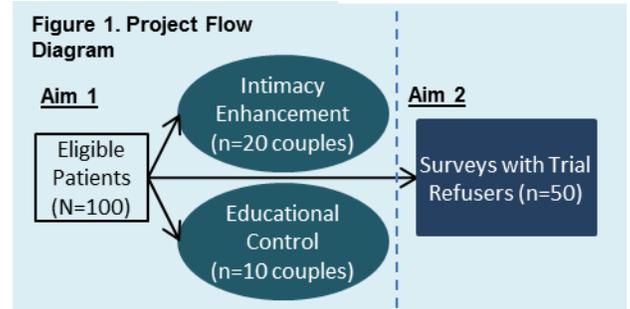
Third, the complexity of sexual problems experienced by breast cancer survivors may discourage providers from raising the issue with their patients,^{44,45} contributing to inadequate identification and treatment. This study will identify the core issues breast cancer survivors face with respect to their sexual QOL and the key areas that should be addressed in

related interventions. An especially unique feature of this investigation is an exploration of barriers to participation and intervention preferences of patients who opt out of the IE intervention pilot trial. The information gained from this aim will directly inform the development of a range of interventions addressing these concerns and is thus likely to be of considerable utility to researchers. Moreover, equipped with available efficacious interventions to offer their patients, breast cancer providers may be more likely to raise the issue of sexual QOL and provide appropriate support. Therefore, the findings of this study will have significant implications for both research and clinicians aiming to improve the care and outcomes of breast cancer survivors.

4.0 Study Design

4.1 Study Overview

The main objective of this study is to pilot test the IE intervention for breast cancer survivors and their partners (See Figure 1). In Aim 1, we will pilot test the IE intervention for feasibility, acceptability, and preliminary efficacy in a small randomized controlled trial in 30 couples. In Aim 2, we will identify barriers to participation and intervention preferences for study-eligible patients who opt out of the pilot trial through brief, structured exploratory orally-administered surveys.



4.2 Recruitment Methods

4.2.1 Recruitment and Reimbursement

Number of subjects per year projected at FCCC	Total number of subjects at FCCC	Total number of subjects overall:	Number of subjects nationally or internationally (if applicable)	Number of subjects at collaborating institutions (if applicable)
Up to: 50	Up to: 80	110	0	0

The human subjects in this entire project include approximately 80 breast cancer patients (N=30 for Aim 1; N=50 for Aim 2) and 30 spouses or partners of breast cancer patients (Aim 1) who will be asked to provide their time and personal information as part of the study, for a total of approximately 110 participants. A lower RC target accrual is 50 (30 patients in Aim 1; 20 patients in Aim 2), and an upper RC accrual goal is 90 (30 patients in Aim 1; 60 patients in Aim 2). We have included Temple University Hospital and School of Medicine as possible recruiting sites and will consider recruiting Temple University Hospital patients if our recruitment could benefit from this addition.

Breast cancer patients are chosen for the study population because breast cancer patients experience sexual concerns and addressing these concerns may improve patients' intimate relationships and quality of life. We will enroll as many "intervention refusers" as possible until we reach our goal of 30 couples into the intervention study, and will stop enrolling "intervention refusers" to Aim 2 once we have reached this goal. While we anticipate approximately 50 study-eligible patients will refuse the trial, it is possible that a smaller number of eligible patients will refuse the trial before we reach our target of 30 couples enrolled in the trial. Thus the number of patients in Aim 2 may differ slightly from our estimate.

4.2.1.1 Patient Contact and Screening

Study candidates will be recruited (a) over the telephone using a study letter sent after identification of appropriate candidates through providers' schedules, or after identification through the Fox Chase Cancer Registry, (2) through in-person clinic recruitment, and (3) through advertisements in clinic and patient areas (e.g., education and resource

room). 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. The initial contact will be conducted with approval from the treating physician/provider (e.g., NP) and will be from the research team and/or the treating provider. For patients identified through the Registry, lists of potentially eligible candidates will be approved by the patients' physician prior to sending the introductory letter. 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 (see Patient Screening Script in Appendix) 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. 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 are currently using many similar items, including the sexual concerns screening item, in protocol 14-833 and have had success with these screening items. Medical record review will confirm the patients' breast cancer diagnosis, stage, and treatment status, as described in the screening script (or in pre-screening).

Patient eligibility screening will occur privately due to the sensitive nature of the questions. 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 (see Patient Screening Script in Appendix).

To ensure adequate understanding of the study by both members of the couple prior to consenting, a study team member must speak personally with both members of the couple and 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.

If the patient is eligible and is interested in 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 no specific eligibility criteria for the partner except age ≥ 21 , which will be determined during the patient's screening. A Partner Introductory Script is also included in the Appendix, to guide the recruiter discussion with the partner, once the patient gives permission to contact the partner.

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. 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).

4.2.1.2 Reimbursement

4.2.1.2.1 Reimbursement for Aim 1 (intervention study)

Participants will receive \$25 for completing pre- and post-intervention assessments (total=\$50 per couple). Compensation will be provided in the form of gift cards. Gift cards will be mailed to participants once both members of the couple have completed either the baseline or the post-treatment online survey. Once the study team members have

verified that the couple has completed the appropriate surveys, a member of the study team will call the participants to confirm that they have received the gift card and the study team member will document this in our research files.

4.2.1.2.2 Reimbursement for Aim 2 (developmental surveys)

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. Patients will either receive these in person or will be mailed them, if the survey takes place over the telephone. Regardless of the method of reimbursement, a research team member will confirm receipt of the compensation and will document this in our research files.

4.3. Inclusion and Exclusion Criteria

Overall, eligible patients for this study will be adult (≥ 21 years) partnered breast cancer patients who have completed active treatment for Stage I-III non-recurrent breast cancer between 6 months and 5 years prior who report sexual concerns (see Table 2). Patients’ spouses or partners must also be ≥ 21 years old.

Table 2. Inclusion Criteria
<ul style="list-style-type: none"> • Female • Age ≥ 21 years • Has diagnosis of non-recurrent stage I-III breast cancer • Completed active treatment (e.g., chemotherapy, radiation therapy, surgery) 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 ≥ 21 • Lives with a romantic partner ≥ 6 months • Score of ≥ 3 on Patient Care Monitor Sexual Concerns screening item⁴⁶ • No hearing impairment in patient or partner
Exclusion Criteria
<ul style="list-style-type: none"> • Not able to speak English, as stated in medical record or as observed by study team member • ECOG Performance score > 2 OR too ill to participate as judged by physician/in medical record • Overt cognitive dysfunction or psychiatric disturbance such as suicidal ideation or severe mental illness, as observed or judged by the researcher, referring source, or other qualified observer. • Past history of any cancer other than non-melanoma skin cancer • Currently participating in couple/marital therapy • 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 history of breast or gynecological cancer, as such patients may have prior sexual complaints and have different needs. Similarly, those with another concurrent cancer treatment are excluded. Pregnant patients are also excluded because they may have different sexual function and sexual concerns. Patients 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. Finally, patients who are too ill, as determined through an ECOG score, medical record, or provider, are excluded because participants are asked to engage in behavioral exercises between intervention sessions and patients who are too ill may not be able to participate fully in such study activities. 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 below in Table 2.

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

No exclusions will be made for any part of the investigation based on sexual orientation, which means that same-sex couples may participate in the pilot trial and those in non-heterosexual relationships may participate in Aim 2.

4.4 Study Data Collection and Measures

4.4.1 Medical Data Collection (Aim 1)

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 (See Medical Records Data Collection Form in Appendix). The data abstraction will be performed by Sharon Schwartz, a Nurse Practitioner and Co-Investigator on our study, or another member of the study team trained or supervised by Ms. Schwartz, and entered into our de-identified databases. This medical chart review is documented in the consent form.

4.4.2 Self-Report Data Collection (Aim 1). An overview of study measures and collection time points for participants in Aim 1 (the pilot trial), including number of items in each scale, is in **Table 3**. After consenting, patients and partners will complete pre- and post-intervention outcome measures through a web portal on their home computers using RedCap.

4.4.2.1 Overview of Self-Report Data Collection (Aim 1).

We have given significant thought to the outcome measures included in our study. First, given recent findings from a sexual QOL intervention study suggesting that long survey batteries may contribute to attrition,⁴⁷ attention was given to selecting brief scales or the abbreviated versions of longer scales whenever possible, such as the 7-item Dyadic Adjustment Scale (vs. the 32-item version). These brief scales are psychometrically sound while decreasing the length of time required of participants. Second, the length of the total survey battery is comparable to those administered in many other similar studies, and is shorter than the battery given in our prior pilot studies in colorectal cancer. Computer-based administration of surveys is often less time-consuming for participants than paper and pencil completion⁴⁸ and reduces the need for time spent in mailing back surveys. Finally, nearly all outcome measures chosen are standardized validated comprehensive scales and many are the gold standard for assessing sexual outcomes (e.g., FSFI/IIEF) and other measures have been used successfully by us in our prior studies (see next paragraph for further explanation of these measures).

We will use RedCap to collect data for Aim 1. 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 the mail using paper and pencil versions of the electronic data forms, printed out by the couple if possible or sent to the couple

by a study team member. If sent through the mail, surveys will be sent (along with consent forms, if necessary) in separate envelopes with instructions to complete these independently from one another.

In addition to our collection of the measures assessing preliminary efficacy of the IE intervention (described below in 4.4.2.2), we will also collect data on patients' and partners' self-efficacy for coping with sexual problems with three items we have used in our recent trial,⁴⁹ and on frequency of patient sexual activities and use of sexual aids assessed with items from the PROMIS Sexual Function measure⁵⁰ to generate effect sizes for the future trial. 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.⁵¹ In addition, we will collect data from both patients and partners on cancer-specific distress,⁵² which has become commonplace in couple-based cancer interventions⁵³ and is important to track given the distress experienced by patients' spouses in confronting their partners' cancer diagnoses.⁵⁴ Demographic characteristics (e.g., age, race/ethnicity) will be assessed through self-report. Additionally, both patients and partners will complete a validated self-report version of the Charlson Comorbidity Index,⁵⁵ which will provide a measure of medical illness comorbidity. This is relevant given the relation between medical illnesses (e.g., cancer, diabetes, heart disease) and sexual function. Particularly for men, but also for women, medical comorbidity is a major determinant of sexual dysfunction.⁵⁶

4.4.2.2 Preliminary Efficacy (Aim 1) will be measured through the following measures shown in **Table 3**, all of which have been validated and psychometrically tested in the context of cancer: **patient and partner sexual QOL outcomes** (sexual function, sexual satisfaction, sexual intimacy, sexual distress) and **relationship outcomes** (emotional intimacy, sexual communication, relationship quality), and **patient psychosocial outcomes** (body image distress, psychological distress). These measures are included in the Self-Report Materials in the Appendix.

4.4.2.3 Feasibility (Aim 1) will be measured through study accrual, attrition, and session completion. Participants will also complete a measure of adherence to study recommendations or review of materials taught within sessions in both conditions through the web portal immediately prior to sessions 2-4 (Materials Review Form; See Self-Report Materials in Appendix) that will help us assess the extent to which engagement in study activities was feasible, while also serving as a potential mediator of change. Couples will be instructed to complete these independently using online survey links. This survey is the same for participants in both conditions and thus does not assess intervention-specific skills or information.

4.4.2.4 Acceptability (Aim 1) will be assessed with the post-intervention assessment through the Client Satisfaction Questionnaire-8 item version (CSQ-8),⁵⁷ a validated measure that elicits the client's perspective on the value of services received. Participants in both conditions will complete the CSQ-8. For comparability with the prior pilot studies, all participants will complete items used in those trials that capture ease of participation, relevance, helpfulness of the intervention, and therapist rapport. In addition, IE participants will be asked about their preferences regarding attending a follow-up "booster" session at the end of the four telephone sessions, which may be implemented in future larger trials using this intervention. Going forward, IE participants will be asked these items as part of the post-treatment assessment. IE participants who have already completed the post-treatment assessment will be contacted by the study team to assess their preferences for a follow-up session. Finally, those assigned to the IE condition will complete items assessing the ease and frequency of use, and helpfulness of skills taught in the intervention (e.g., communication; See Self-Report Materials in Appendix).⁴¹

Table 3. Outcome Measures								
Measure	Construct	# Items	Baseline	Session 1	Session 2	Session 3	Session 4	Post-Treatment
Patient and Partner Sexual QOL Outcomes								
Female Sexual Function Index (FSFI)* ^{58,59}	Sexual function	19/15	X					X
International Index of Erectile Function (IIEF) ⁶⁰								

PROMIS Sexual Satisfaction Items ⁶¹	Sexual satisfaction	5	X					X
Female Sexual Distress Scale-Revised* (FSDS-R) ⁶²	Sexual distress	13	X					X
PAIR Sexual Intimacy Subscale ⁶³	Sexual Intimacy	6	X					X
Beliefs (self-efficacy) ^{64,65}	Self-efficacy	3	X					X
Intimate Activities and Use of Sexual Aids (PROMIS Items) ^{27,61*}	Frequency of sexual activity/use of aids	8	X					X
Patient and Partner Relationship Outcomes								
PAIR Emotional Intimacy Scale ⁶³	Emotional Intimacy	6	X					X
Dyadic Sexual Communication Scale (DSCS) ⁶⁶	Sexual communication	13	X					X
Dyadic Adjustment Scale-7 item (DAS-7)	Relationship quality	7	X					X
Patient Psychosocial Outcomes – ONLY COMPLETED BY PATIENT								
Body Image Scale (BIS) ⁶⁷	Body image distress	10	X					X
Patient Health Questionnaire-9 item (PHQ-9) ⁶⁸	Distress (depression)	9	X					X
Generalized Anxiety Disorder 7-item (GAD-7) ⁶⁹	Distress (anxiety)	7	X					X
Additional Items Completed by Patients/Partners								
Baseline demographic information for patient/partner	Demographic data	12/7	X					
Post-treatment demographic items	Demographic data	2						X
Charlson Comorbidity Index ⁵⁵	Medical comorbidity	11	X					
Impact of Events Scale ⁵²	Cancer-Specific Distress	22	X					X
Sexual Self-View (importance of sexuality to self)	Sexual self-view	2	X					X
<i>Total # of items in baseline scales</i>								
<i>Patients</i>	153							
<i>Partners</i>	95							
Intervention Process Forms (completed individually)								
Program Evaluation Form	Credibility	7		X				
Materials Review Form	Adherence	7			X	X	X	
CSQ-8 ⁵⁷	Acceptability	8						X
Additional Acceptability Questions ^{64,65}	Acceptability	18						X
Skills Assessment ^{**64,65}	Utilization of skills	3						X
Additional Information Completed by Patients								
Post-treatment demographic information	Demographic/medical data	2						X
<i>Total # of items in post-treatment scales</i>								
<i>Patients</i>	169							

<i>Partners</i>	118							
* indicates that patients only complete this measure ** indicates that only IE participants complete this measure								

4.4.3 Self-Report Data Collection (Aim 2)

All data collected from participants in Aim 2 (developmental survey study) will be collected using the Developmental Survey (See Developmental Aim Draft Survey in Appendix), which will be administered verbally, rather than by the patients and is thus in an interview style, or over the web. This survey collects information on patients’ reasons for lack of interest in participating, preferences for resources or programs addressing sexual/intimacy concerns, and race/ethnicity. More information about this survey can be found in section 4.7. 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.

4.5.1 Overview of Randomization and Intervention Conditions (Aim 1)

Couples will be randomized with an allocation ratio of 2:1 to either the IE or the Educational Control (Living Healthy Together) condition, in order to maximize data generated on the active condition, with stratification by age at diagnosis (≤ 45 vs. > 45) using the age obtained by patients during the screening. Because of the broad intimacy targets of this intervention, outcomes may not differ by menopausal status and therefore we will not stratify by this variable. However, because sexual function can differ by menopausal status, we will investigate menopausal status as a possible moderator of outcome in the intervention group for future research.

Randomization will occur once both members of the couple have consented, completed baseline surveys, and are scheduled for their first intervention session. At this time, 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.

4.5.1.2 Interventionists (Aim 1)

All sessions will be conducted by an experienced and trained counselor. The interventionists have Master’s degrees or above (doctorate) in social work or counseling/psychology and are either licensed to engage in clinical services or have equivalent educational background and/or experience. Interventionists also have years of relevant clinical experience including conducting CBT. Some of the current interventionists have also had experience conducting couple therapy sessions on Sharon Manne’s couple-based studies and are thus familiar with utilizing intervention manuals in conducting interventions as part of a research study. Interventionists will be trained to deliver both types of intervention sessions through an in-person training workshop or viewing a recording of the in-person training workshop that will include review of couple therapy approaches and about the topic area, review of study intervention manual and patient handouts, and interactive role plays with feedback. The precise content of each interventionist’s training procedures could differ slightly depending on their prior experience and comfort with the material. Interventionists may also listen to session recordings as a part of their training. All interventionists will be certified by the PI as adequately trained prior to scheduling them for sessions with intervention participants. Regular supervision sessions among the interventionists led by Dr. Reese, the PI and developer of the IE intervention, will be held to ensure adequate quality of the delivered interventions. All supervision sessions are confidential; no identifiable information about participants is retained in supervision records. The quality assurance procedures regarding the delivery of the intervention are described further in section 16.0.

4.5.1.3 Intervention Format (Aim 1)

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.⁶⁴ 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,⁷⁰ and to whom eligibility for this study is limited. Audio calls will be made using Skype (not video calls), cell phone, or landline service to the couple's preferred mobile or landline phone (no Skype username or subscriptions needed for couples) using speakerphone. All sessions will be recorded, and these audio recordings destroyed when the study is completed.

4.5.2 Intimacy Enhancement (IE) Intervention (Aim 1). The proposed IE intervention content is outlined in Table 5 (See Appendix for a draft outline of the intervention)^{41,49} 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 format²⁵ and because couple-based interventions are more effective at improving sexual outcomes in this population.^{30,71} 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 intervention includes both educational content and cognitive and behavioral skills training with the aim of reducing sexual distress and avoidance, increasing coping skills of both patients and partners, and improving physical and emotional intimacy. A unique feature of this intervention is that it addresses a range of both physical and emotional intimacy targets, such as loss of sexual interest and activity, and behavioral couple-based skills to adjust to sexual changes (e.g., sensual touching). Such skills are critical elements of successful programs addressing sexual concerns for breast cancer survivors⁷¹ and Dr. Reese has published previously on an Intimacy Enhancement intervention teaching these skills.^{64,65} Techniques are also included from (a) sex therapy, including sensate focus (sensual touching exercises),⁷² (b) couple therapy (e.g., communication skills),⁷³ and (c) cognitive behavioral therapy (e.g., restructuring negative/inflexible thoughts).^{51,74} A cornerstone of the IE intervention is an approach to coping with sexual difficulties proposed previously by the PI that emphasizes flexibility in thoughts and behaviors.⁵¹ 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.

Session	Topic	Education Topics	Skills	Home practice
1 (75 min)	Understanding Impact of BC on Sex and Intimacy	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)	Communication about Sex/ Intimacy	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)	Problem-solving and Changing Thoughts	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 and Preparing for Challenges	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	1. Complete post-intervention measures

4.5.3 Educational Control Condition (Aim 1). The Educational Control condition (called Living Healthy Together or LHT) is a stringent control condition which equates with the active condition for time and attention from a therapist, and

receiving education from a credible source. However, in contrast with the IE condition, LHT focuses on education and support rather than skills training (See Appendix for outline) and it also does not include specific education on sexuality or intimacy. Like the IE condition, the LHT condition follows a structured outline for each session though the discussions can depend on participants' interests and the sessions are designed to last as long as IE sessions.

Topics to be discussed include breast cancer and its treatments (e.g., staging, common treatments, side effects), sleep and energy, stress and stress management, nutrition/diet. All of these topics are relevant to sexual function⁷⁵ and therefore make up an appropriate and highly credible control condition for patients screened for sexual concerns. Unlike in the IE condition, participants in LHT will not be explicitly encouraged to engage in particular activities or management strategies but rather will be encouraged to read the materials given to them provided at each session. Their engagement with the material will be assessed at each session using the Materials Review Form, just as in the IE condition.

4.6 Time Commitment for Participants (Aim 1)

On average, we anticipate that participants will take about 6 weeks to complete the study from consent to post-treatment assessment. Baseline and post-treatment surveys will take approximately 30-45 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 allow for the four sessions to be completed within 12 weeks (from the start of the first session). Completion of the post-treatment survey by both members of the couple should occur 2-7 days after completing the last intervention session (but if they need more time to complete it, we will allow this). Thus, the minimum study duration would be approximately 5 weeks, and the maximum study duration would be approximately 14 weeks.

4.7 Developmental Survey (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, or over the web, depending on the method of recruitment) assessing their reasons for not participating and preferences for interventions addressing sexual concerns (See Developmental Aim Draft Survey in Appendix).

The administration of this survey will likely occur at the time of screening but may occur at a later time if necessary (but no later than one month post-screening, if a patient is willing but unable to complete the survey at the time of screening). This survey will be administered only once and contains 8 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 through the web, the recruiter will send the patient a link for completing the online survey and the items will be identical regardless of the format.

Patients will be asked the survey questions privately; if necessary, partners will be asked to leave the room to ensure patient privacy. This is particularly important because one item specifically asks whether the patient would like the partner included in programs. If the patient does not want to be interviewed alone, we will not proceed.

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

5.0 Risks to Participants

The major risks for study subjects are (1) discomfort at answering study questions during the focus group, on surveys, or during intervention sessions and (2) loss of privacy or confidentiality. Due to the protections we will have in place, we believe these risks to be minimal. Additionally, there is some risk that couples in Aim 1 who are distressed may

experience additional distress during intervention discussions about sensitive topics. Based on our previous experience with couple-based interventions, we expect this risk 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

While we hope that the Intimacy Enhancement intervention will benefit patients and partners, there may be no direct benefit to the study participants. It is possible that the Intimacy Enhancement intervention may address patients' sexual concerns and therefore have a beneficial effect on patient and partner sexual quality of life outcomes, relationship outcomes, and on patient psychosocial outcomes. Couples in the Educational Control condition may also benefit from having the support of a professional for an equivalent length of time and from the educational material provided. Findings from the pilot trial will inform the design of a larger multi-site trial which has the potential to improve patient health and quality of life, once disseminated. Findings from the developmental aim may inform future research on interventions that may be well-suited to addressing the sexual concerns of a large number of breast cancer survivors. 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, especially in light of the dearth of available evidence-based interventions addressing sexual concerns for this population.

7.0 Provisions to Maintain the Confidentiality of Data

7.1. General 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, 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. Overview of Consent Processes

If a participant consents to participate in Aim 1, the couple-based intervention study, they are consenting to completing survey data online about their physical, sexual, and emotional health, to allow us to obtain limited medical data from their 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.

Those who participate in Aim 2 are consenting to providing information about their reasons for lack of participation and intervention preferences on a brief survey interview.

9.1.1. Consent Process for Aim 1

First, the recruiter or 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 that the participant can participate in the current study regardless of his/her response to this item.

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 the 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.

Only English speaking patients will be enrolled. Children will not be enrolled in this study.

9.1.2 Consent Process for Aim 2

After screening and refusal of the pilot 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 (see Developmental Aim Consent Script in Appendix).

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 the 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, the participant and his or her partner may be asked if they would be willing to remain in the study for data collection in four weeks which will enable us to conduct intent-to-treat analyses (or the length of time that would coincide with the end of their treatment sessions).

If a patient's disease recurs or needs to start active treatment during the study, they will be allowed to remain on the study, if they choose, and this information will be tracked in their 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

Not applicable.

13.0 Statistical Analysis

13.1. Statistical Analyses for Aim 1

13.1.1. Primary and Secondary Outcome Variables

13.1.1.1. Primary outcomes are feasibility and acceptability of the study. Feasibility will be measured through study accrual, attrition, and session completion. Acceptability is measured using the CSQ-8 (See Self-report Materials in Appendix).

13.1.1.2. Secondary outcomes are preliminary efficacy of the study in patient and partner sexual outcomes (sexual function, sexual satisfaction and intimacy, sexual distress), patient and partner relationship outcomes (emotional intimacy, sexual communication, relationship quality), and patient psychosocial outcomes (body image distress, psychological distress). The measures assessing these outcomes can be found in Table 3 above.

13.1.2. Analyses

13.1.2.1. Feasibility. Analyses will be descriptive. We aim for accrual at a rate of 30% to match our prior study,⁴² but a rate over 20% will be acceptable. Attrition at levels greater than those found by similar studies⁴⁷ (e.g., 30%) will be considered unfeasible. 80% of participants completing the 4 sessions is considered adequate.

13.1.2.2. Acceptability. Analyses will be descriptive. Adequate acceptability of the study will be indicated by a group median score ≥ 28 on the CSQ-8,⁷⁶ representing a fairly high score across a range of studies, including a behavioral marital therapy randomized controlled trial.⁷⁷

13.1.2.3. Preliminary efficacy. Preliminary efficacy of the IE intervention on patient and partner sexual outcomes, patient and partner relationship outcomes, and patient psychosocial outcomes will be established using an effect size calculation method that is appropriate for small sample sizes³⁴ that our team has employed previously.^{34,49} First, pre-post changes scores are calculated for each participant. Second, the between-group effect size is calculated by subtracting the mean control group change score from the mean IE group change score. This difference is then divided by the standard deviation of the pooled change score. Given that multilevel dyadic analyses are questionable in small sample sizes,⁷⁸ we will consider dyadic analyses, including actor-partner effects,⁷⁹ in the planned R01.

Because our primary goal through the analyses for this aim is to generate effect sizes for a larger planned study, we will conduct the analyses described above using data from study completers. However, we will also attempt to obtain post-treatment surveys even for couples who have dropped out of the study during the intervention phase, to allow us to conduct intent-to-treat analyses. Patients without any post-treatment data will have baseline data used in these analyses.

13.2. Statistical Analyses for Aim 2

13.2.1. Primary Outcomes

The primary outcomes from the intervention refuser surveys are the candidates' responses regarding barriers/reasons for choosing not to participate and preferences for resources or interventions. Analyses of responses will focus on identifying the areas for consideration in future intervention development and will be descriptive in nature.

13.2.2. Secondary Outcomes

There are no secondary outcomes.

13.2.3. Analyses

Analyses of responses will focus on identifying the areas for consideration in future intervention development. We will conduct descriptive analyses such as measures of central tendency when possible from numerical responses (i.e., frequencies, means, standard deviations). Open-ended responses will be analyzed qualitatively and descriptively when possible (e.g., frequency of certain responses).

13.2.4. Sample Size Calculations

The objective of this study is to pilot test the newly adapted Intimacy Enhancement study and to allow us to calculate effect sizes that will inform a larger R01 trial that is expected to follow from this study. We selected 30 couples to participate in this trial because it is a large enough sample to provide ample pilot data while maintaining adequate feasibility in the time allotted. Further, we have chosen a 2:1 allocation to the Intimacy Enhancement condition, which allows us to gather greater information from participants in this condition, our primary interest, relative to the Couple Education condition.

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 will contain the contact information for the PI and the Institutional Review Board (IRB). A DSMB is not required for the current study.

15.0. Adverse Event Reporting

Because of the nature of the research as involving procedures without significant risk (e.g., surveys; telephone discussions) there are unlikely to be any serious adverse events and adverse events are likely to be rare. Possible risks include feeling worried, anxious, or concerned during questionnaire completion or during the intervention sessions. Adverse events include significant distress or psychological reactions experienced during the study procedures (e.g., in the case of severe untreated depression, suicidal intent, or extreme marital conflict). 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.

Any unexpected or adverse event that occurs during data collection or study procedures is reported immediately to the Principal Investigator, who is responsible for documenting all adverse events with the FCCC IRB 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 provide the participant with a referral to appropriate services. At FCCC counselors in the Department of Social Work 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 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. If 3 or more 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.

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.

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 16.1.1 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 16.1.2. Fourth, the PI 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 (See Self-Report Materials in Appendix) 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 call the conditions by their names (Intimacy Enhancement; Living Healthy Together) 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 minimum of a Master’s degree in a mental health profession (e.g., social work) 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 (4.5.1.2). 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 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.

16.1.1. 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 an 8-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 through RedCap (See Self-Report Materials in Appendix), separately by patients and partners using online links. They will be instructed by the interventionists not to share any of their responses with the interventionist. Data from this form will be analyzed after overall study data collection is completed to compare the credibility across the groups.

16.1.2. 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 (e.g., the PI, Laura Porter, a consultant and expert in couple-based interventions) will listen to a random sample of 15-20% 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.

16.2. 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 Informed Consent documents

18.0. References

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19.0. Appendices

- Consent Forms
 - Web-based version of Aim 1 Consent
 - Paper version of Aim 1 Consent
 - Aim 2 Developmental Survey Consent Script
 - Aim 2 Developmental Survey Written Consent Document
 - Request for Waiver of Documentation of Consent (for Aim 2)
- Surveys or Data Collection Tools
 - Self-Report Materials
 - Developmental Survey
 - Medical Records Data Collection Form
- Recruitment Materials
 - Study Brochure
 - Study Flyer
 - Patient Recruitment Screening Script
 - Partner Recruitment Introductory Script
 - Study Introductory Letter
- Intervention Content
 - Intimacy Enhancement Outline
 - Living Healthy Together Outline