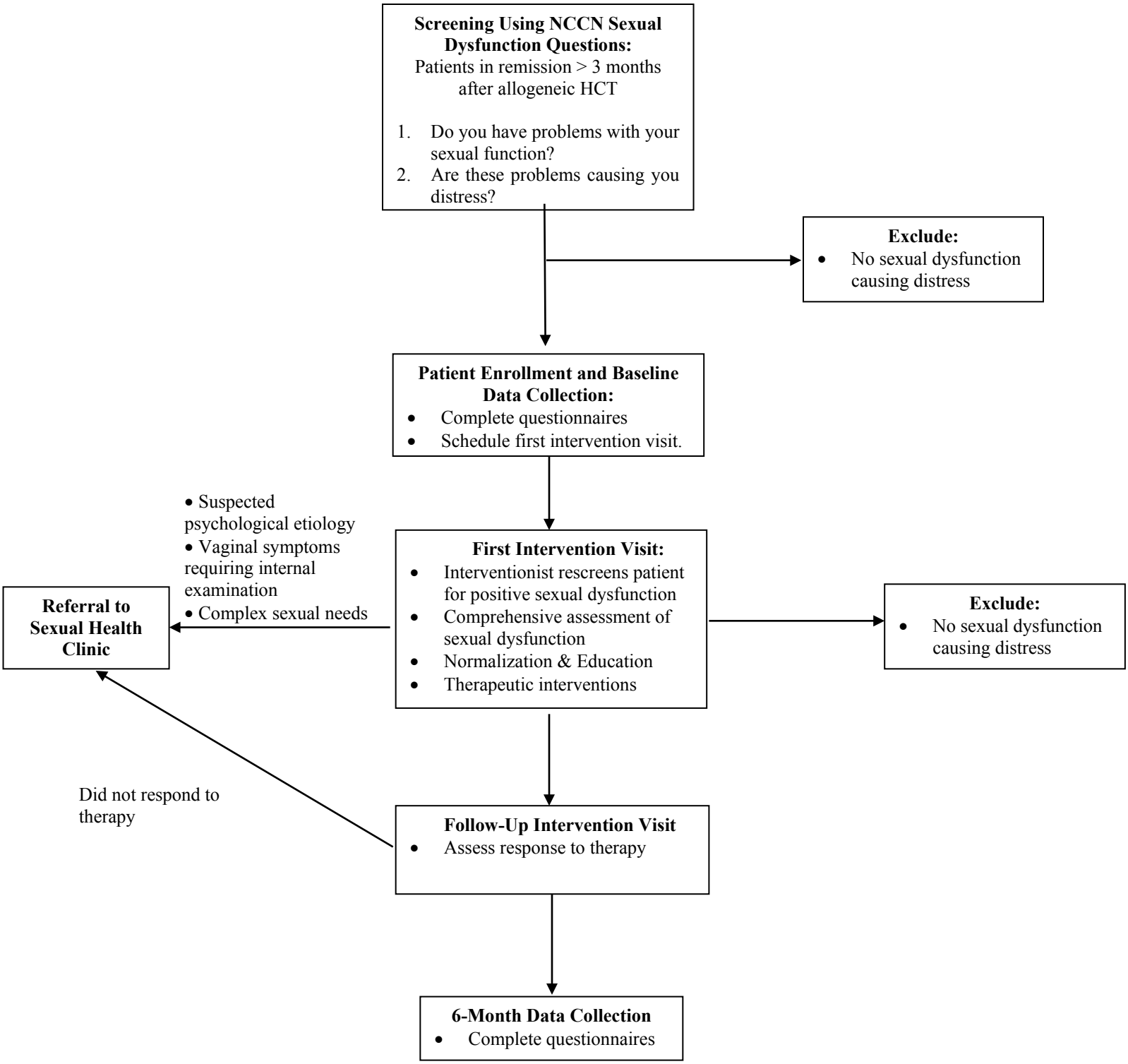
SECTION 1: Protocol Schema



SECTION 2: BODY OF PROTOCOL

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1 Introduction

1.1 Overview

The goal of this project is to develop and evaluate a multimodal sexual dysfunction intervention for survivors of allogeneic hematopoietic stem cell transplantation (HCT). The National Comprehensive Cancer Network (NCCN) identifies sexual dysfunction as a major issue facing cancer survivors that negatively impacts their quality of life (QOL) and mood. Allogeneic HCT survivors, like many cancer survivors, experience a significant and drastic deterioration in their sexual function that persists for many years following their therapy. In fact, sexual dysfunction is the most common and persistent long-term complication of HCT, adversely affecting patients' QOL, mood, and intimacy. Nearly half of HCT survivors are dissatisfied with the quality of their sexual life. Moreover, studies have clearly demonstrated that sexual dysfunction is associated with worse QOL, fatigue, emotional well-being, relationship satisfaction, and psychological distress. Thus, many allogeneic HCT survivors endure a significant deterioration in their sexual function, which adversely impacts their QOL and mood, and increases the overall morbidity of their treatment.

The etiology of sexual dysfunction post-transplant is multifactorial and includes problems with sexual desire and pleasure, hormonal deficiencies, vaginal and penile alterations secondary to graft-versus-host-disease (GHVD), delayed or absent orgasm and/or ejaculation, pain with intercourse, erectile dysfunction, and psychological problems such as anxiety, depression, and changes in body-image. Thus, an intervention that assesses a wide range of physical and psychological conditions is needed to address the range of sexual problems seen in this population.

Unfortunately, interventions to improve sexual function in HCT survivors are lacking. Additionally, clinicians are reluctant to address sexual function with their patients due to their lack of training and discomfort in engaging in these conversations. Given the well-documented burden of sexual dysfunction that allogeneic HCT survivors face, there is a compelling need to develop interventions that encourage clinicians to discuss sexual health issues with their patients, using a comprehensive and multimodal approach to address their diverse sexual needs.

In this project, we will develop and evaluate the efficacy of a multimodal sexual dysfunction intervention for allogeneic HCT survivors. The proposed project will proceed in two phases. During phase 1, we will conduct a prospective pilot study assessing the feasibility and preliminary efficacy of the intervention in improving patients' sexual function, QOL, and mood. During phase 2, we will conduct qualitative interviews with patients who completed the intervention to explore their perceptions of its acceptability, content, and efficacy, and the optimal timing for its delivery during their survivorship course. Data from this work will help inform a large-scale randomized study of a sexual dysfunction intervention for allogeneic HCT survivors.

The proposed project will assess an innovative and sexual dysfunction intervention that has the potential to substantially enhance the care of survivors of hematologic malignancies. Moreover, such an intervention can be adapted for use with other cancer survivors struggling with sexual dysfunction after their treatment. By implementing a multimodal intervention to improve sexual function, we aim to enhance the QOL, mood, and intimacy of cancer survivors.

1.2 Background and Significance

The NCCN identifies sexual dysfunction as a major issue affecting many cancer survivors.[1] For allogeneic HCT survivors, sexual dysfunction is the most common and persistent long-term complication affecting patients' QOL, mood, and intimacy.[2-5] Nearly half of HCT survivors are dissatisfied with the quality of their

sexual life.[6] Studies have clearly documented worse psychosexual functioning in HCT survivors compared to healthy subjects and to those treated with chemotherapy alone.[2,3] Notably, 45% of men reported a significant decline in quality and quantity of sexual function at 6 months, 1, 2, and 3 years after HCT compared to prior to transplant.[5] Moreover, 40% of women are not sexually active at any time point post-HCT. [5] **Thus, many allogeneic HCT survivors endure a significant and rapid deterioration in sexual function, which persists for many years after their treatment.**

Sexual health plays a central role in one's identity, QOL, and self-esteem;[2] thus it is not surprising that sexual dysfunction causes increased distress and negatively impacts the QOL of cancer survivors.[7-10] Research has shown that sexual function is associated with QOL, fatigue, relationship satisfaction, emotional well-being, anxiety, and depression.[3,11] **Therefore, improving patient's sexual function post-transplant may have significant effects on their QOL and psychological distress, and decrease the overall morbidity of allogeneic HCT.**

Allogeneic HCT survivors experience diverse problems affecting their sexual function.[2] Sexual complications include decreased libido, decreased pleasure, vaginal alterations, erectile and ejaculatory dysfunction, delay or absence of orgasm/ejaculation, premature menopause, sex hormonal deficiencies, dyspareunia, and infertility.[3,12-17] Moreover, GVHD can affect the genital tract leading to vaginal stenosis and scarring. It can also cause scarring, adhesions and long-term injury to blood vessels with resulting arterial insufficiency, which manifests as erectile dysfunction in men and potentially anorgasmia in women. Finally, transplant itself can result in dermatologic changes and increased skin sensitivity affecting the genital tract.[14,17,18] Lastly, problems with body-image, self-confidence, fear of disease recurrence, anxiety, depression, and concerns about infertility all play a major psychological role in affecting sexual function in transplant survivors.[19-22] **Sexual dysfunction post-transplant is multi-factorial and requires a multimodal approach to care.**

Despite its prevalence, health care providers are reluctant to address sexual dysfunction with cancer survivors.[4,16,23,24] In addition to insufficient time during an outpatient clinic visit, clinicians also site lack of training and discomfort as barriers to discussing sexual dysfunction with their patients.[1,25] Interestingly, patients who participated in a discussion with their health care provider about sexuality reported fewer sexual functioning problems at 3 years post-transplant compared to those who did not have any discussions.[4] **Interventions are critically needed to improve the rate and content of conversations between clinicians and patients about sexual functioning post-HCT.**

In addition to encouraging clinicians to discuss sexual health issues with their patients, we must develop interventions to improve patients' sexual function. Despite the tremendous well-documented burden of sexual dysfunction on allogeneic HCT survivors, interventions to improve sexual function are lacking.[2] Importantly, given the diversity of problems affecting sexuality in allogeneic HCT survivors, interventions must include a comprehensive assessment and a multimodal approach to address the diverse needs of this population.[2] **While effective strategies exist to treat both female and male sexual dysfunction, interventions are critically needed to integrate these strategies into the care of allogeneic HCT survivors with an emphasis on their specialized needs.**

In this project, we aim to develop and evaluate a multimodal sexual dysfunction intervention for allogeneic HCT survivors. We will assess the feasibility and preliminary efficacy of the intervention in improving sexual function, QOL, and mood in transplant survivors. We will also use qualitative methods to explore patient's perception of the acceptability, content, and efficacy of the intervention and their preferences

for the timing of its delivery in the survivorship course. **Data from this work will help inform a large-scale randomized study of a sexual dysfunction intervention for allogeneic HCT survivors.**

1.3 Preliminary Studies

Quality of Life and Mood of Patients and Family Caregivers During Hospitalization for HCT[26]
We conducted a prospective longitudinal study of patients undergoing HCT to assess the impact of transplant hospitalization on patients' QOL and mood. We enrolled 97% of potentially eligible patients undergoing HCT. We administered patient reported measures to assess QOL and mood both weekly during their transplant hospitalization and at a follow up outpatient clinic visits, with a missing data rate of only 20%. Of note, we did not have any missing data from the outpatient clinic visits. This work demonstrates our research team's success in conducting longitudinal studies on patients undergoing HCT. Additionally, the findings from this work were used to develop a palliative care intervention specifically addressing the needs of patients undergoing HCT, which is currently being tested in a randomized clinical trial. Therefore, our team has prior experience developing innovative interventions targeting the needs of a particular population.

Randomized Study of a Targeted Palliative Care Intervention in Patients Hospitalized for HCT
We are currently conducting a randomized trial to evaluate the impact of a palliative care intervention on patients' QOL, mood, and symptom burden during hospitalization for HCT. The study opened for enrollment in August 2014 and to date we have enrolled 57 of 60 (95%) eligible participants. Only one participant (2.5%) withdrew and did not complete all patient reported measures. This work highlights our research team's experience conducting supportive care interventions in patients undergoing HCT. Moreover, it demonstrates our ability to successfully recruit and enroll transplant patients in intervention studies.

2 Objectives

Quantitative Objectives and Hypotheses:

1. **To evaluate the feasibility of implementing a multi-modality sexual dysfunction intervention for allogeneic HCT survivors.**

   Hypothesis: We will be able to recruit 75% of patients who screen positive for sexual dysfunction causing distress to participate in a sexual dysfunction intervention, and 80% of participants will attend at least one additional follow-up or referral visit.

2. **To determine the preliminary efficacy of the intervention in improving sexual function, QOL, and mood.**

   Hypothesis: Participants will have improved sexual function, QOL, and mood at 6 months post-intervention compared to baseline.

Qualitative Objective:

1. **To explore patients' perception of the acceptability, content, and efficacy of the intervention, as well as the optimal timing for intervention delivery during the survivorship course.**

3 Research Subject Selection

3.1 Study Subject Selection:

We will recruit 53 allogeneic HCT survivors who are at least 3 months post-HCT and without evidence of disease from Massachusetts General Hospital bone marrow transplant clinic to participate in this prospective pilot study.

Patients Eligibility criteria:

1. Adult patients (≥18 years) with hematologic malignancy who underwent an allogeneic HCT at least 3 months prior to study enrollment.
2. Ability to speak English or able to complete questionnaires with assistance required from an interpreter or family member.
3. Positive screen for sexual dysfunction that is causing distress based on the NCCN survivorship guidelines.

Patient Exclusion criteria:

1. Patients with relapsed disease post-HCT.
2. Significant psychiatric or other co-morbid disease, which the treating clinician believes prohibits the patient's ability to participate in the informed consent procedures.

4 Research Subject Entry

4.1 Study Research Subject Entry

A total of 53 patients with hematologic malignancies who are 3 months after allogeniec HCT will participate in this study. All MGH transplant oncologists and nurse practitioners have agreed to participate in the study.

The research team will screen the weekly transplant clinic schedule to identify potentially eligible patients. The research staff will then inform the transplant clinician that the patient is eligible and inquire about any concerns regarding his or her study participation. If the transplant clinician has any objections regarding the patients' participation, we will document the reasons and not approach those individuals. If there are no concerns regarding study participation, the research team will attach a notification form to the patient's check-in sheet upon arrival to the transplant clinic. The form will instruct the transplant clinician to screen the patient for sexual dysfunction using the two-question approach based on the updated 2015 NCCN survivorship guidelines: 1) do you have problems with sexual function?; and 2) Are these problems causing you distress? The transplant clinician will then offer study participation for those individuals who screen positive for sexual dysfunction causing distress. If patients are interested in study participation, a member of the research team will then will review the consent form with potential participants, which will clearly detail the nature of the study procedures, the time requirements, and frequency of the self-report questionnaires. The research team member will obtain written informed consent from participants and provide them with a copy of the signed consent form.

Study participants will complete baseline self-report assessments at the time of obtaining informed consent for the study or within the 72 hour window from study enrollment. Patients who provide informed consent and complete baseline questionnaires will then be registered with QACT and scheduled for their first study intervention visit on the same day as their regularly scheduled subsequent follow-up visit.

4.2 Registration and randomization procedures

4.2.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

4.2.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.2.3 General Guidelines for Other Investigative Sites: Not applicable

4.2.4 Registration Process for Other Investigative Sites: Not applicable

5 Study Design and Methods

5.1 Design/ Study Type

The proposed project will proceed in two phases. During phase 1, we will conduct a prospective pilot study assessing the feasibility and preliminary efficacy of the intervention in improving patients' sexual function, QOL, and mood (quantitative objectives). During phase 2, we will conduct qualitative interviews with patients who completed the intervention to explore their perceptions of its acceptability, content, and efficacy, and the optimal timing for its delivery during their survivorship course (qualitative objective).

***5.2 Study Procedures**:*

We will recruit 53 patients with hematologic malignancies 3 months after allogeneic HCT who report having sexual dysfunction causing distress for this study. Once written informed consent is obtained, patients will receive an outpatient multimodal sexual dysfunction intervention . The interventionist will rescreen the patients at the beginning of their initial visit. If patients no longer experiences sexual dysfunction before their initial study visit, they will considered ineligible for the study as they are no longer experiencing distress relating to sexual dysfunction. Because these patients have already signed consent, they will count towards accrual, but will no longer be eligible to participate in the intervention.

Prior to patients' enrollment on this study, we will train a total of two transplant clinicians regarding how to assess and address sexual dysfunction in the transplant clinic. Dr. Don Dizon is the Director of the MGH Cancer Center Sexual Health Clinic and a world-renown expert on sexual dysfunction in cancer survivors. He will first provide transplant clinicians with reading materials regarding how to assess and address sexual dysfunction. The transplant clinicians will review this literature prior to their didactic training sessions with Dr. Dizon. Dr. Dizon will then conduct two training sessions with the same two transplant clinicians prior to study enrollment to ensure they acquire the necessary skills to implement the sexual dysfunction intervention in the transplant clinic. One transplant MD and one experienced transplant nurse practitioner (NP) will be responsible for implementing the intervention in the transplant clinic.

Dr. Dizon will first conduct a two-hour didactic training session with the transplant clinicians, focusing on the following areas:

1) How to perform a comprehensive sexual function assessment: This includes a comprehensive assessment of prior and current sexual history with an emphasis on identifying the causes of sexual dysfunction. Dr. Dizon will review the sexual function questionnaires that he utilizes in the Sexual Health Clinic to identify causes of sexual dysfunction. These questionnaires will be completed by all study participants at baseline and will be available to the transplant clinicians to review prior to seeing the patients for an intervention visit. Dr. Dizon will review how to assess various aspects of sexual function including libido, pleasure, orgasm/ejaculation, vaginal symptoms (for women), painful intercourse, erectile and ejaculatory function, premature menopausal symptoms, signs and symptoms of hormonal deficiencies, and psychological barriers to intimacy including body-image issues, self-confidence, anxiety, depression.

2) Normalization of the topic and patient empowerment and education: Dr. Dizon will also train transplant clinicians regarding the optimal ways to discuss this sensitive topic. He will review strategies to normalize the topic, create a comfortable environment for patients to ask questions, and empower them to become an active part of addressing their sexual health needs. Dr. Dizon will focus on the language he utilizes in his clinic when speaking to patients regarding their sexual function.

3) Therapeutic interventions for sexual dysfunction in men and women: Dr. Dizon will also outline therapeutic strategies to address the various causes of sexual dysfunction in men and women. For full details regarding these interventions, please see section 5.5 (therapeutic interventions).

4) When to refer patients for additional expertise: Dr. Dizon will teach transplant clinicians to identify patients with more complex sexual dysfunction needs including suspected psychological etiology for sexual dysfunction, relationship or intimacy problems, and women with significant vaginal symptoms requiring a vaginal examination.

Dr. Dizon will then conduct an additional 1-hour didactic session with the transplant clinicians. This additional training session will involve case presentations to augment the clinicians' understanding of the various causes and treatments of sexual dysfunction.

Finally, the transplant clinicians will also attend two sexual health clinic sessions with Dr. Dizon to obtain clinical experience in evaluating and treating patients with sexual dysfunction.

5.3 Selection of study instruments

- ***Demographics:***

Patients will complete a demographic questionnaire at baseline detailing their age, sex, race, ethnicity, religion, relationship status (FC will specify their relationship with patients), educational level, annual household income, and living situation [appendix A].

- ***Participant-reported measures:*** We will administer the following questionnaires at baseline and 6 months after enrollment:
- **Male sexual function:** We will utilize the PROMIS Sexual Function and Satisfaction measures for men including the following domains: Global satisfaction with sex life, interest in sexual activity, erectile function, and orgasm [Appendix B].[27]

- **Female sexual function:** We will utilize the Female Sexual Function Index (FSFI), which identifies problems with sexual desire and interest, sexual arousal, lubrication, reaching orgasm, pain with intercourse, and emotional closeness during sexual activity [Appendix C].[28]

- **Patient-QOL:** We will use the Functional assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) to assess QOL, which has been validated for use in patients undergoing HCT [Appendix D].[29]

- **Mood:** We will use the Hospital Anxiety and Depression Scale (HADS)[30] to assess symptoms of psychological distress (depression and anxiety) [Appendix E], and the PHQ-9[31] to assess major depressive syndrome [Appendix F].

- **Qualitative Data Collection:** We will also conduct qualitative interviews with approximately 8 male and 8 female patients from the phase I participant pool to participate in the second phase. Participants must complete the 6-month post intervention assessment in phase I prior to enrolling in phase II. We will use a semi-structured interview guide to 1) explore patients' perception of the acceptability and content of the sexual dysfunction intervention; 2) explore patients' perception of the efficacy; and 3) identify the optimal timing of intervention delivery during the survivorship course. We will audi-record the interviews, transcribe them by Audio Transcription Center in Boston, MA, and code and analyze them using NVivo 10 software.

5.4 Administration and timing of self-reported measures:

We will collect and enter all patient-reported data electronically using Research Electronic Data Capture (REDCap). The REDCap Survey is a tool for building and managing online surveys. Vanderbilt University, in collaboration with a consortium of institutional partners, has developed this software and workflow methodology for electronic collection and management of research and clinical trial data. Our research team has extensive experience using REDCap and will create and design the surveys in a web browser, with institutional information technology support. The REDCap Survey system offers secure, HIPAA compliant, web-based

applications that provide an intuitive interface for participants to enter data, with real-time validation rules at the time of entry.

Participants will use tablet computers to complete questionnaires in clinic. If any participants refuse or are unable to complete the questionnaires on the computer, they will be permitted to use hard-copy paper versions. Participants who do not have a regularly scheduled clinic visit will be provided with remote access to REDCap system or paper-based questionnaire for home administration. The research team will contact patients twice to remind them to complete and return the surveys. If study participants fail to complete the surveys within the expected time point, we will report the data as missing and document the reason for incompletion. Table 1 details the schedule for administering the self-report measures. All participants will complete baseline evaluation within 72 hours of study enrollment. All participants will then have a second evaluation at 6 months (+/- 2 weeks).

Table 1 **Participant Measures**	**Baseline (**within 72 hours of informed consent)	**6 months from enrollment** (+/- 2 weeks)
Demographics	X	
Male sexual function	X	X
Female sexual function	X	X
QOL (FACT-BMT)	X	X
Depression/Anxiety (HADS)	X	X
Depression (PHQ-9)	X	X

5.5 Description of Intervention

The intervention will include the following two components: 1) assessing and treating sexual dysfunction in the transplant clinic; and 2) referring patients with more complicated needs to the sexual health clinic. During the first component, patients will attend up to two intervention visits with the trained transplant clinicians to assess and address sexual dysfunction. If patients do not respond to the intervention delivered in the transplant clinic and/or they are deemed to have more complex sexual health needs, they will be referred to the sexual health clinic for additional expertise (second component). Therefore, the intervention entails both the intervention visits in the transplant clinic as well as any additional visits in the sexual health clinic.

1. ***Primary sexual dysfunction intervention in the transplant clinic:*** We developed this multimodal intervention in collaboration with Dr. Don Dizon based upon 1) a comprehensive review of the NCCN guidelines on survivorship; and 2) a systematic review of the literature on sexual dysfunction affecting men and women.

   We will schedule all consented participants for a clinic visit with one of the three trained transplant clinicians specifically addressing sexual dysfunction, including the following elements:

   A. ***In-depth sexual function assessment:*** The trained transplant clinicians will conduct a comprehensive sexual function assessment based on the NCCN survivorship guidelines. They will utilize the baseline questionnaires completed by participants to identify factors contributing to sexual dysfunction. Female participants will complete the Female Sexual Function Index (FSFI) and male participants will complete the PROMIS Sexual Function and Satisfaction measures for men. Additionally, the transplant clinicians will evaluate psychological causes for sexual dysfunction including self-confidence, body image issues, anxiety, and depression. Lastly, the transplant clinicians will evaluate patients for hormonal deficiencies,

GVHD affecting the skin and genitals, medication side-effects or substance abuse, and other comorbidities that may affect sexual function in men and women.

B. ***Normalization, Empowerment, and Education:*** The transplant clinicians will provide information about sexuality in order to normalize these issues and affirm the importance of the topic. In addition, the transplant clinicians will educate patients on issues relevant to sexual health, including but not limited to the prevalence of sexual dysfunction post HCT. They will also elicit participants' concerns regarding engaging in such a conversation. They will provide participants with educational materials focusing on sexual dysfunction in cancer survivors including the potential etiologies and contributing factors as well as helpful suggestions for management. The transplant clinicians will empower patients to ask questions and utilize these resources.

C. ***Therapeutic Interventions:*** Additional interventions instituted in the transplant clinic will be directed towards the various etiologies affecting sexual function. Additional intervention visits may also be conducted over the phone to minimize the stress and travel of participants. Specifically:

For men with:

- Signs and symptoms suggestive of testosterone deficiency[32]: These include erectile dysfunction, low sexual desire, and delayed ejaculation, as well as other signs such as visceral obesity, reduced muscle mass, and low bone mineral density. Transplant clinicians will screen for testosterone deficiency. If total testosterone <230 ng/dL, they will start testosterone supplementation.
- Erectile dysfunction[32]: Transplant clinicians will counsel male participants regarding risk factor modification including smoking cessation, weight loss, increasing physical activity, and avoiding access alcohol consumption. In addition, the transplant clinicians will prescribe and titrate phosphodiesterase inhibitors for the treatment of erectile dysfunction.

For women with:

- Signs and symptoms suggestive of menopause or treatment-induced amenorrhea[25]: These include vaginal symptoms, including dryness and dyspareunia, as well as more systemic signs, such as hot flushes and irritability. If present, transplant clinicians will offer participants hormone replacement therapy. However, acknowledging that some patients will not be interested in hormone replacement therapy, transplant clinicians will offer non-estrogenic therapies including gabapentin and/or selective serotonin inhibitors.

- Dyspareunia: Patients will require a pelvic examination for complaints of dyspareunia and they will be referred to the sexual health clinic.

For men and women with:

- Skin GVHD: Transplant clinicians will treat signs of genitopelvic GVHD with local corticosteroid and/or tacrolimus creams.
- Medication-induced sexual dysfunction: Transplant clinicians will identify potential offending agents and discontinue them if possible. When medications causing sexual dysfunction are necessary, the clinicians will prescribe treatment to enhance sexual function such as phosphodiesterase inhibitors.
- Low desire secondary to depression treatment: Patients on antidepressant medication may experience a lack of desire. For these patients, transplant clinicians will offer the use of phosphodiesterase inhibitors.

We will schedule all participants for a 4-week follow-up intervention visit and/or referral to the MGH Cancer Center sexual health clinic (see specialty referral to the sexual health clinic). The objective of the 4-week follow-up visit is to assess participants' responses to specific therapies. 4-week follow-up visits can be conducted over the phone or in clinic at MGH. If participants do not report any improvement in their sexual dysfunction during the follow-up visit based on the transplant clinician's assessment, they will be considered non-responders. The transplant clinicians will then refer them to the sexual health clinic within 30 days.

2. ***Specialty referral to the sexual health clinic:*** During the first transplant clinic visit, the transplant clinicians will refer the following participants directly to the MGH Cancer Center sexual health clinic:

    - Suspected psychological etiology for sexual dysfunction (self-confidence, body-image issues, depression, anxiety, and/or fear of disease recurrence).
    - Suspected relationship and intimacy problems.
    - Women participants with vaginal dryness, itching, and/or pain with intercourse: These women will require a vaginal examination to differentiate atrophic vaginitis from GVHD.
    - Participants with complex sexual needs as determined by the transplant clinicians.

Dr. Don Dizon will evaluate all participants referred to the sexual health clinic at the MGH Cancer Center. He will conduct a comprehensive sexual assessment and individualize his treatment approach based on the needs of the study participants. Possible interventions will include: the use of lubricants, vaginal moisturizers, topical lidocaine, estrogen creams for atrophic vaginitis, local corticosteroid therapy for GVHD, dilators, testosterone to enhance male/female sexual desire, continuous and intermittent phosphodiesterase inhibitors, vacuum-assisted erection devices, penile self-injections, intraurethral prostaglandins, and referrals for penile prosthesis.[25] Moreover, Dr. Dizon will triage and refer participants with psychological causes of sexual dysfunction to psychiatry, cognitive behavioral therapy, and/or couples or sex therapy as appropriate.

5.6 Data Collection

As discussion previously in section 5.4 (Administration and timing of self-reported measures), we will collect and enter all patient-reported data electronically using Research Electronic Data Capture (REDCap). Our research team has extensive experience using REDCap and will create and design the surveys in a web browser, with institutional information technology support. The REDCap Survey system offers secure, HIPAA compliant, web-based applications that provide an intuitive interface for participants to enter data, with real-time validation rules (automated data type and range checks) at the time of entry.

5.7 Description of Study Process

5.7.1 Study Instrument Administration

Patients will use tablet computers to complete baseline and 6-month questionnaires in clinic. If participants refuse or are unable to complete the questionnaires on the computer, they will be permitted to use paper versions. Participants who are not present in the cancer center during the period of data collection will be provided with remote access to the REDCap system or paper-based questionnaires for home administration. The research team will contact patients twice to remind them to complete and return the surveys. If study participants fail to complete the surveys within the expected time point, we will report the data as missing and document the reason for incompletion.

5.7.2 Intervention Administration

Patients will be scheduled to meet with the trained transplant clinician for the sexual dysfunction intervention on the same day as their regularly scheduled follow-up visit. After the initial intervention visit, the participants will be scheduled for a 4-week follow-up visit with the trained transplant clinician and/or referral to the sexual health clinic. The objective of the 4-week follow-up visit is to assess participants' responses to specific therapies. If participants do not report any improvement in their sexual dysfunction during the follow-up visit based on the transplant clinician's assessment, they will be considered non-responders. The transplant clinicians will then refer them to the sexual health clinic within 30 days. Once referred to the sexual health clinic, patients and Dr. Dizon may schedule additional visits as needed.

5.7.3 Special Concerns

We do not anticipate any complications with this study. We have administered questionnaires to over 100 patients in previous studies and there have been no complications.

5.7.4 Compensation

We will provide no compensation for participating in this study.

5.8 Adverse Reactions and Their Management

5.8.1 Reporting Adverse or Unanticipated Events

This study is evaluating the feasibility and preliminary efficacy of a sexual dysfunction intervention with minimal chance of causing harm. We have administered study questionnaires to over 100 patients in previous studies with no adverse events. While some of the items on the questionnaires are sensitive in nature, no previous study participants have withdrawn from the study.

5.8.2 Anticipated Reactions

Should participants exhibit or express distress or anger, they will be reassured by the Research Assistant that they need not answer any questions which they find upsetting. They will also be reminded that study participation is voluntary. If participants remain distressed, both the Principal Investigator and the transplant oncology team will be notified. Should several participants express distress over an individual item, the research team will review the questionnaire and contact the IRB to consider removing it from the study.

If participants report severe distress or suicidal ideations during the interview or while completing any of the questionnaires, the research team will inform the participants that there is an obligation to report this to the patients' primary oncology team and the transplant social worker. The oncologist and social worker will then determine the need to involve psychiatry and take further action as deemed necessary. The research team will review sensitive items regarding suicidal ideations immediately at the time of survey administration and will report any suicidal ideations to the oncology provider and social worker promptly prior to participants' departure from clinic.

5.8.3 Reaction Management

Should participants experience distress, the outpatient transplant social worker will be contacted to see the participant. All staff are familiar with how to contact the social worker via pager. The transplant social workers at MGH have all agreed to be available to respond and help with the management of any adverse reactions.

If participants report suicidal ideations during the interview or while completing any of the questionnaires, the research team will inform study participants that there is an obligation to inform their oncologist and the

transplant social worker. The oncologist and social worker will then determine the need to involve psychiatry and take further action as deemed necessary.

6 Ethical and Legal Issues

*6.1 **Confidentiality***

All patient information will remain confidential and stored on Partners computers and in REDCap. Identifiers such as name will only be used during the initial data retrieval process and can be destroyed once all data records have been obtained and data analysis completed.

Participants' response to survey questions will remain confidential unless there are active suicidal ideations confirmed by the research team. Under these circumstances, as clearly stated in the patient consent form, participants will be informed that the research team has a formal obligation to inform the oncologist and the transplant social worker due to concern for participants' safety. The oncologist and the social worker will then determine the need to involve psychiatry and/or take further action as deemed necessary.

7 Statistical Analysis

*7.1 **Primary and secondary endpoints:***

7.1.1 *Primary endpoint:* The primary endpoint of the proposed study is feasibility. We chose the sample size for this study based on the feasibility of completing the project during the proposed timeframe. The proposed intervention will be deemed feasible if it meets the following criteria:

- At least 75% (95% confidence interval +/- 12%) of patients screening positive for sexual dysfunction causing distress agree to participate in the study and attend the first scheduled intervention visit.

- At least 80% of participants (95% confidence interval +/- 11%) attend at least two intervention visits (either in the transplant clinic or specialty referral).

7.1.2 Secondary endpoint: The following secondary endpoints represent the preliminary efficacy endpoints

1. Change in sexual function from baseline to 6 months
2. Change in QOL from baseline to 6 months
3. Change in psychological distress scores (HADs and PHQ-9) from baseline to 6 months
4. To qualitatively 1) explore patients' perception of the acceptability and content of the sexual dysfunction intervention; 2) explore patients' perception of the efficacy; and 3) identify the optimal timing of intervention delivery during the survivorship course.

7.2 ***Sample Size Calculation:***

As stated in section 7.1.1, the primary endpoint of the proposed study is feasibility. We chose the sample size for this study based on the feasibility of completing the project during the proposed timeframe. The proposed intervention will be deemed feasible if it meets the following criteria:

- At least 75% (95% confidence interval +/- 12%) of patients screening positive for sexual dysfunction causing distress agree to participate in the study and attend the first scheduled intervention visit.

- At least 80% (95% confidence interval +/- 11%) of participants who attend the first visit will also attend at least one additional follow-up visit and/or specialty referral.

These estimates are informed by our prior supportive care trial in HCT patients. We are currently conducting a study evaluating a palliative care intervention for patients undergoing HCT. In this study, we have successfully enrolled 40/44 (90.9%) of potentially eligible participants. Only one participant withdrew and did not complete the longitudinal follow-up (2.5%). Given the sensitive nature of the topic, we are making a conservative estimate of feasibility that 60% (0.75 X 0.80) of patients screening positive for sexual dysfunction will attend the first scheduled intervention visit and at least one additional follow-up and/or specialty referral visit.

We will also select approximately 8 male and 8 female patients from the phase I participant pool to participate in the qualitative phase of this study. We chose approximately 8 male and 8 female patients for the qualitative study to ensure that we have sufficient number of patients to achieve thematic saturation. Additionally, we will purposefully select participants with varying times from their HCT to capture participants throughout the survivorship trajectory. Therefore, we will select approximately 5-6 participants who enrolled in the study within each of the following timeframes: 1) less than one year after HCT; 2) greater than one year, but less than two years after HCT; and 3) more than two years after HCT.

7.3 ***Stratification factors and intervention allocation plan for randomized studies:*** not applicable

7.4 ***Definition of an allowance in design for unevaluable/ineligible participants:*** No applicable

7.5 ***Analysis Plan:***

We will report baseline demographic and clinical characteristics of all study participants. The primary endpoint of the proposed study is feasibility. The proposed intervention will be deemed feasible if it meets the following criteria:

- At least 75% of patients screening positive for sexual dysfunction causing distress agree to participate in the study and attend the first scheduled intervention visit.

- At least 80% of participants who attend the first visit will also attend at least one additional follow-up visit and/or specialty referral.

The secondary endpoints will include determining the preliminary efficacy of the intervention in improving QOL, mood, and sexual dysfunction (objective 2). We will utilize the paired t-test to examine changes in QOL (FACT-BMT), depression and anxiety (HADS, PHQ-9), and sexual dysfunction (PROMIS for males, and FSFI for females) scores from baseline to 6 months after initial intervention visit. In addition to examining

participants' mood scores continuously as described above, we will also transform scores into dichotomous outcomes reflecting the presence or absence of clinically significant depression and anxiety symptoms ((HADS-subscale score > 7)) and major or other depressive syndromes (PHQ-9). For the PHQ-9, a major or other depressive syndrome is diagnosed if a patient reports at least two of the nine symptoms of depression, with one of the symptoms being anhedonia or depressed mood.[31] We will use the McNemar test on paired proportion to examine the change in these dichotomous outcomes from baseline to 6 months. We chose 6 months to assess the preliminary efficacy of the intervention as this would allow participants sufficient time to attend at least two intervention visits targeting their sexual dysfunction within a reasonable timeframe for project completion.

We will analyze the qualitative data using qualitative methodologies described by the NIH Best Practices for Mixed Methods Research in Health Science by Miles and Huberman's text, Qualitative Data Analysis.[33] The analyses will entail a multi-step process using coding and content analysis to explore 1) patients' perception of the acceptability and content of the sexual dysfunction intervention; 2) patients' perception of intervention efficacy; and 3) the optimal timing of intervention delivery during the survivorship course. This will involve coding to structure data into categories and creating groups according to the broader issues or themes. We will identify major and minor themes within each content area and we will extract and highlight messages. Two independent coders will examine discrepant, unexpected, or unclear data until agreement is reached. To assure the trustworthiness of our findings, we will take steps to maximize reliability and credibility including: investigator triangulation (using a multidisciplinary team of investigator), and team debriefs of the interview content.

8 References:

1. Network NCC: National Comprehensive Cancer Network: Survivorship Version 2.2014,
2. Thygesen KH, Schjodt I, Jarden M: The impact of hematopoietic stem cell transplantation on sexuality: a systematic review of the literature. Bone Marrow Transplant 47:716-24, 2012
3. Watson M, Wheatley K, Harrison GA, et al: Severe adverse impact on sexual functioning and fertility of bone marrow transplantation, either allogeneic or autologous, compared with consolidation chemotherapy alone: analysis of the MRC AML 10 trial. Cancer 86:1231-9, 1999
4. Humphreys CT, Tallman B, Altmaier EM, et al: Sexual functioning in patients undergoing bone marrow transplantation: a longitudinal study. Bone Marrow Transplant 39:491-6, 2007
5. Syrjala KL, Kurland BF, Abrams JR, et al: Sexual function changes during the 5 years after high-dose treatment and hematopoietic cell transplantation for malignancy, with case-matched controls at 5 years. Blood 111:989-96, 2008
6. Molassiotis A, van den Akker OB, Milligan DW, et al: Gonadal function and psychosexual adjustment in male long-term survivors of bone marrow transplantation. Bone Marrow Transplant 16:253-9, 1995
7. Bober SL, Varela VS: Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol 30:3712-9, 2012
8. Donovan KA, Thompson LM, Hoffe SE: Sexual function in colorectal cancer survivors. Cancer Control 17:44-51, 2010
9. Laumann EO, Paik A, Rosen RC: Sexual dysfunction in the United States: prevalence and predictors. JAMA 281:537-44, 1999
10. Morreale MK: The impact of cancer on sexual function. Adv Psychosom Med 31:72-82, 2011
11. Molassiotis A, van den Akker OB, Milligan DW, et al: Quality of life in long-term survivors of marrow transplantation: comparison with a matched group receiving maintenance chemotherapy. Bone Marrow Transplant 17:249-58, 1996

12. Socie G, Stone JV, Wingard JR, et al: Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med 341:14-21, 1999

13. Tierney DK: Sexuality following hematopoietic cell transplantation. Clin J Oncol Nurs 8:43-7, 2004

14. Syrjala KL, Roth-Roemer SL, Abrams JR, et al: Prevalence and predictors of sexual dysfunction in long-term survivors of marrow transplantation. J Clin Oncol 16:3148-57, 1998

15. Syrjala KL, Langer SL, Abrams JR, et al: Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. J Clin Oncol 23:6596-606, 2005

16. Claessens JJ, Beerendonk CC, Schattenberg AV: Quality of life, reproduction and sexuality after stem cell transplantation with partially T-cell-depleted grafts and after conditioning with a regimen including total body irradiation. Bone Marrow Transplant 37:831-6, 2006

17. Heinonen H, Volin L, Uutela A, et al: Gender-associated differences in the quality of life after allogeneic BMT. Bone Marrow Transplant 28:503-9, 2001

18. Yi JC, Syrjala KL: Sexuality after hematopoietic stem cell transplantation. Cancer J 15:57-64, 2009

19. Hensel M, Egerer G, Schneeweiss A, et al: Quality of life and rehabilitation in social and professional life after autologous stem cell transplantation. Ann Oncol 13:209-17, 2002

20. Bruner DW, Calvano T: The sexual impact of cancer and cancer treatments in men. Nurs Clin North Am 42:555-80; vi, 2007

21. Barton-Burke M, Gustason CJ: Sexuality in women with cancer. Nurs Clin North Am 42:531-54; vi, 2007

22. Weber CS, Fliege H, Arck PC, et al: Patients with haematological malignancies show a restricted body image focusing on function and emotion. Eur J Cancer Care (Engl) 14:155-65, 2005

23. Bober SL, Carter J, Falk S: Addressing female sexual function after cancer by internists and primary care providers. J Sex Med 10 Suppl 1:112-9, 2013

24. Forbat L, White I, Marshall-Lucette S, et al: Discussing the sexual consequences of treatment in radiotherapy and urology consultations with couples affected by prostate cancer. BJU Int 109:98-103, 2012

25. Dizon DS, Suzin D, McIlvenna S: Sexual health as a survivorship issue for female cancer survivors. Oncologist 19:202-10, 2014

26. El-Jawahri A, Traeger, L., Kuzmuk K., et al: Qualit yof life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. Cancer in press, 2014

27. Flynn KE, Lin L, Cyranowski JM, et al: Development of the NIH PROMIS (R) Sexual Function and Satisfaction measures in patients with cancer. J Sex Med 10 Suppl 1:43-52, 2013

28. Baser RE, Li Y, Carter J: Psychometric validation of the Female Sexual Function Index (FSFI) in cancer survivors. Cancer 118:4606-18, 2012

29. McQuellon RP, Russell GB, Cella DF, et al: Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. Bone Marrow Transplant 19:357-68, 1997

30. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70, 1983

31. Kroenke K, Spitzer RL, Williams JB: The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16:606-13, 2001

32. Montorsi F, Adaikan G, Becher E, et al: Summary of the recommendations on sexual dysfunctions in men. J Sex Med 7:3572-88, 2010

33. Miles M HA: Qualitative data analysis: a sourcebook of new methods. Beverly Hills, CA, Sage Publications, 1984