Supplementary Materials

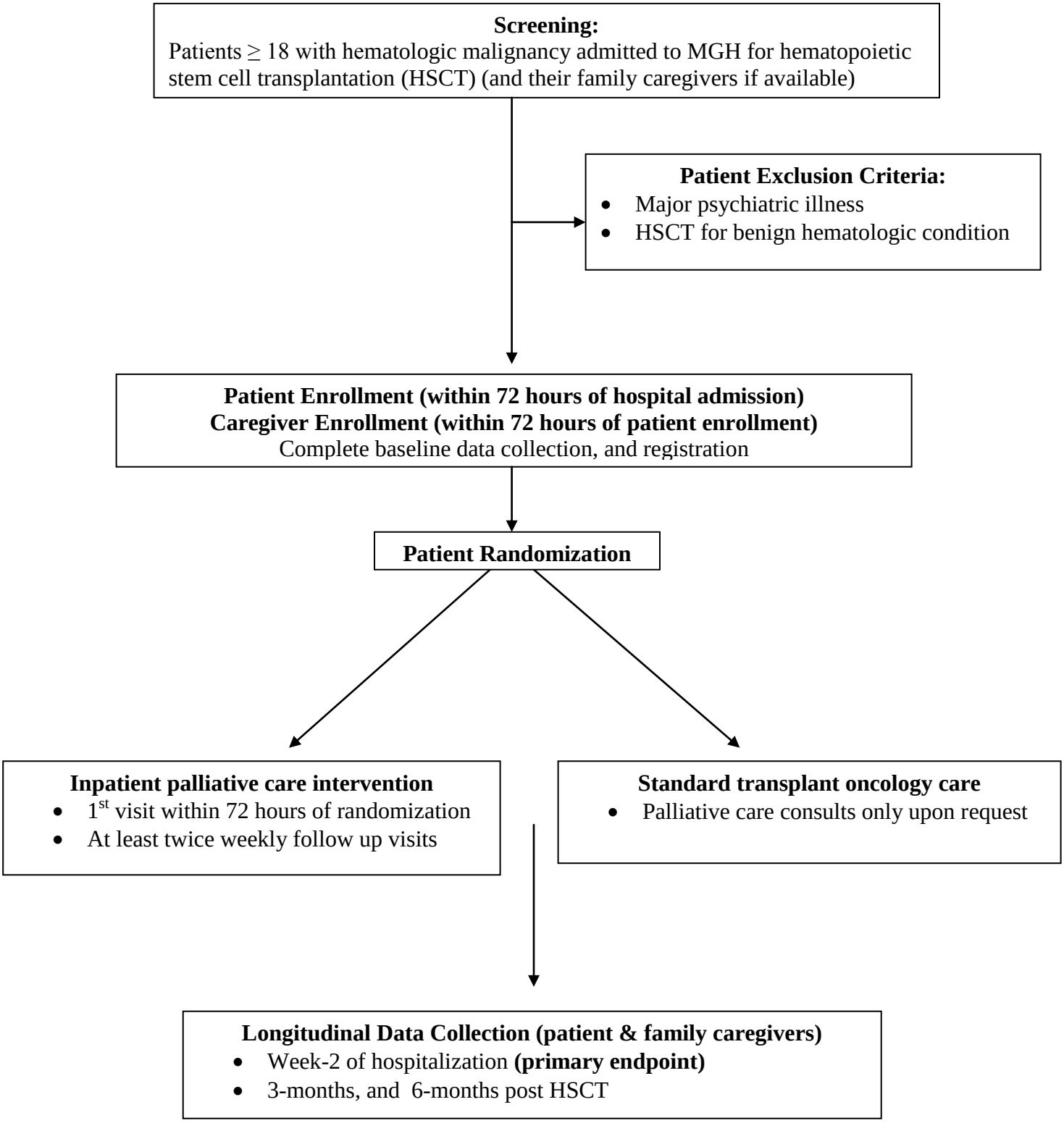
Supplement A: Study Protocol

Supplement B: Palliative care intervention manual

Supplementary tables 1 and 2

Study Protocol

SECTION 1: Protocol Schema



SECTION 2: BODY OF PROTOCOL

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1 Introduction

1.1 Overview

The goal of this study is to assess the impact of a targeted inpatient palliative care intervention on quality of life (QOL), and symptom burden in patients admitted to the hospital for hematopoietic stem cell transplantation (HSCT) and their family caregivers. During their hospitalization for HSCT, patients with hematologic malignancies experience significant physical symptoms due to chemotherapy-induced toxicities and early post-transplant complications. These symptoms, along with the physical isolation patients experience during the transplantation, contribute to the significant deterioration in their QOL and mood throughout their hospital stay. Furthermore, the distress patients experience during transplantation often persists and has long-term QOL and psychological consequences, further exacerbating the morbidity of HSCT.

The family caregivers of patients hospitalized for HSCT also experience significant emotional, psychological, and physical distress resulting in deterioration of their QOL during their loved ones transplant. The stress of witnessing their loved ones struggle with toxicities during HSCT is emotionally draining and distressing. Furthermore, as patients are hospitalized for several weeks, family caregivers must assume all household and financial responsibilities for a prolonged period. Therefore, the patients' hospitalization for HSCT is also a challenging period for family caregivers, with the potential to negatively impact their QOL and mood.

While palliative care clinicians are increasingly asked to care for patients with solid tumors, they are rarely consulted to assist in the management and support of patients with hematologic malignancies. Given the physical and psychological burdens that patients and their family caregivers experience during hospitalization for HSCT, inpatient palliative care services are ideally suited to provide the necessary supportive care for this population. Palliative care clinicians are highly specialized in complex symptom management and thus better equipped than oncology providers to manage the challenging toxicities experienced by patients during HSCT. Additionally, HSCT recipients are at high risk for future complications including morbidity from chronic graft-versus-host-disease and risk of disease relapse. Integrating palliative care early in the care of transplant recipients provides an opportunity to engender trust and develop longitudinal relationships with this population who may benefit additionally from palliative care expertise in the future.

Providing palliative care during a patients' hospitalization for HSCT offers a unique opportunity to (1) enhance patients' and family caregivers' QOL during the transplant; (2) improve long-term QOL and psychological outcomes for HSCT survivors; and (3) build collaborative relationships with transplant clinicians to allow further integration of palliative care to meet the needs of HSCT survivors at various point in their illness trajectory. We conducted a pilot longitudinal study to comprehensively delineate the needs of patients hospitalized for HSCT and their family caregivers in order to design a targeted inpatient palliative care intervention for this population. We now propose to conduct the first prospective randomized study to assess the impact of a targeted inpatient palliative care intervention on patient and family caregiver reported QOL and symptom burden.

1.2 Background and Significance

Patients undergoing HSCT experience significant physical and psychological symptom burden:

High dose chemotherapy followed by HSCT has become a commonly utilized component of conventional treatment for patients with hematologic malignancies. In fact, HSCT has increased in frequency because of its demonstrated efficacy for a larger number of disease indications and safety profile in older patients.[1]

Patients undergoing HSCT tolerate significant transplant-related-toxicities and side effects with the hope of curing their underlying malignancy.[2-5] Despite the acute morbidity of HSCT, the majority of research has focused primarily on the long-term physical and functional burdens associated with the medical procedure.[1,6] Multiple studies have shown that, even years after HSCT, many patients experience impaired physical, emotional, and role functioning compared to population norms.[7-25]

While numerous studies highlight the considerable long-term burdens associated with surviving HSCT, little published data exist on the challenges that patients and family caregivers endure during the acute hospitalization period.[24-26] Specifically, the immediate impact of HSCT on patients' QOL as well as physical and psychological symptoms at the time of hospitalization has not been well described in the literature.[27-29] During HSCT, patients receive high-dose chemotherapy with multiple associated toxicities leading to distressing physical symptoms and a prolonged hospitalization.[30] This acute phase of illness likely carries the highest degree of morbidity as patients cope with the underlying disease and lingering symptoms from prior therapies. Even before hospital admission, many patients experience marked symptoms such as pain, fatigue, depression, and anxiety.[31-36]

In patients undergoing HSCT, the side effects and symptom burden during the course of hospitalization likely vary over time. For example, patients undergoing autologous HSCT are more likely to experience nausea during chemotherapy administration, while fatigue is more prominent later in the hospitalization.[24] The lack of longitudinal studies elucidating the trajectory of patients' physical and emotional wellbeing prompted us to conduct a prospective longitudinal study to provide a more detailed description of the experience of patients undergoing HSCT. The findings of this study, highlighted in the preliminary studies section, depict a high physical and psychological symptom burden that varied during the hospitalization course. These symptoms were associated with a tremendous deterioration in QOL, which persisted during the hospitalization.

Symptoms during HSCT hospitalization can predict short and long-term psychological outcomes:

In addition to a significant physical symptom burden, we also noted a high degree of depressive symptoms during the course of hospitalization for HSCT in our prospective observational study. The extent of physical symptoms experienced by transplant recipients may be the primary driver for higher psychological distress over time.[30] Studies have shown that uncontrolled physical symptoms can instigate and exacerbate depression in patients with advanced cancer.[37-39] Furthermore in patients undergoing HSCT, worsening physical health status has been correlated with higher depressive symptoms and impaired QOL.[30,40] Therefore an inpatient palliative intervention focused on addressing the symptoms of patients undergoing HSCT may lead to significant improvement in their mood and QOL.

The physical and psychological symptoms of HSCT recipients may also have long-term consequences both in terms of psychological and QOL outcomes.[31,41-44] Several studies suggest that patients' physical and psychological distress during transplantation may predict their long-term psychological morbidity and the risk of transplant-related complications.[31,41-43] Many HSCT survivors develop depression and symptoms of post-traumatic stress disorder as a consequence of their hospitalization for HSCT.[6,12,45-50] In fact, as many as 41% of HSCT survivors experience persistent PTSD symptoms up to 10 years post transplantation.[51-54] These long-term psychological implications can further add to the morbidity of the transplant procedure. For example, depression at 6 months post-HSCT is a strong predictor of higher 1- and 3-year post-transplant mortality.[44,55,56] Therefore, improving patients' symptoms and QOL during hospitalization for HSCT may have significant long-term effects on QOL, psychological distress, and overall morbidity of HSCT survivors.

The family caregivers are also negatively impacted by patients' hospitalization for HSCT:

The family and close friends of patients undergoing HSCT are also substantially impacted by the patient's illness. In particular, stress from supporting a loved one through HSCT may adversely affect the social and emotional well-being of the family caregiver.[57] Moreover, watching a loved one struggle with the side effects during HSCT can be emotionally challenging. Depending on the age and relationship of the family caregiver, supporting a loved one through HSCT may represent a significant disruption to the caregiver's personal life including difficulties in maintaining responsibilities at home and work.[57-59]

Few studies have examined the impact of HSCT on the QOL of family caregivers.[57,60,61] As with investigations of patients' QOL, most of these studies have focused on the long-term impact of supporting a loved one through HSCT, overlooking the burden to caregivers during the acute phase of treatment. Nonetheless, the existing data and our preliminary findings do point to high levels of distress and vulnerability in the family caregivers of patients undergoing HSCT.[57,58,60-64]

Interventions to address the needs of patients and caregivers during HSCT are lacking:

Due to the paucity of data on the physical and psychological burden experienced by patients and their family caregivers during hospitalization for HSCT, investigators to date have tested only a few supportive care interventions during this time period.[65-68] Two studies examined the role of exercise to improve the experience of patients during HSCT and have demonstrated improvement in physical function and well-being.[65,66] In addition, others have shown that psychosocial interventions can improve patient-reported pain during HSCT hospitalization.[67,68] However, no interventions have been developed to improve the overall QOL, physical and psychological symptoms of patients hospitalized for HSCT and their family caregivers.

Inpatient palliative care can improve symptoms and quality of care in patients with advanced cancer:

Although large, well-controlled randomized trials are not abundant in the literature, prior research has demonstrated that palliative care improves symptoms and quality of care for patients in the inpatient setting.[69-71] The number of palliative care programs in the United States continues to rise, and the majority of academic medical centers and large community hospitals have palliative care consult services available to provide inpatient care.[72] Palliative care clinicians frequently receive referrals to support patients with incurable solid tumors in the hospital setting, but they are rarely consulted to assist in the care of patients with hematologic malignancies.[73] Cultural barriers and misconceptions have contributed to the lack of collaboration and involvement of palliative care services in the care of patients undergoing HSCT.[73] Considering that patients with hematologic malignancies are likely to receive aggressive cancer care, this population could greatly benefit from such palliative care services.[74-76] In addition, symptom management in patients undergoing HSCT is quite complex and may be beyond the scope of expertise of many oncology-trained clinicians.[77] Thus, further research is critically needed to evaluate the potential benefits of palliative care in the inpatient setting for those undergoing HSCT and their family caregivers.[78]

Developing a population-specific palliative and oncology care model is crucial to its success:

Based on a number of recent studies by our group and others, researchers have demonstrated increasing interest in developing integrated palliative and medical care models for the use in multiple clinical specialties including cardiology, neurology, and oncology.[79-81] While the emerging data on concurrent palliative and oncology care are encouraging, poorly defined interventions and outcomes measures have hampered the field substantially.[69,70] These methodological shortcomings have resulted in many inconclusive or negative studies, impeding the development of well-conceptualized and sufficiently powered randomized studies. We utilized rigorous methodological design to comprehensively delineate the needs of patients undergoing HSCT and their family caregivers. Therefore, the findings from our prospective pilot study permit us to create a well-articulated intervention tailored to the specific needs of

patients undergoing HSCT. By developing a high-quality targeted intervention and testing its efficacy in a rigorous manner, we will enable the broad dissemination of this innovative model of integrated palliative care.

We propose the first targeted inpatient palliative care intervention in patients undergoing HSCT:
Due to the immense symptomatic burden and prolonged hospitalization, patients hospitalized for HSCT and their family caregivers represent an ideal population to target with an inpatient palliative care intervention. We propose to conduct the first randomized study testing the impact of a targeted inpatient palliative care intervention on QOL and physical and psychological symptoms of patients during hospitalization for HSCT. We will also examine the effect of the inpatient palliative care intervention on the long-term QOL, and psychological outcomes of HSCT recipients. Finally, we will test whether the family caregivers' QOL and mood can be improved with the integration of inpatient palliative care services for the care of their loved ones during hospitalization for HSCT. The palliative care intervention being tested in this study is built upon a strong methodological foundation and the findings of a rigorous longitudinal study, which described comprehensively the experience patients undergoing HSCT. The intervention utilized in this project is therefore used with specific guidelines that can be reliably administered, reproduced, and measured in future studies.

The ultimate goal of our research agenda is to establish the usefulness of integrating palliative care early in the trajectory of HSCT recipients. We anticipate that that our inpatient palliative care intervention will significantly alleviate the physical and psychological symptoms and improve the QOL of patients undergoing HSCT during the acute hospitalization period as well as in the long term at 6 months post-HSCT. Additionally, by integrating palliative services in the care of patients undergoing HSCT, we hope to improve the QOL and psychological distress of their family caregivers. Finally, integrating palliative care with standard transplant care engenders trust between the two services overcoming cultural barriers that long stood in the way of collaboration. Ultimately, the introduction of early palliative care during the most vulnerable period for HSCT recipients offers an instrumental opportunity for building longitudinal relationships between palliative care services and HSCT survivors who are at high risk for morbidity, and mortality in the future.

1.3 Preliminary Studies

1.3.1 Physical and Psychological Symptom Burden and Quality of Life during Hospitalization for HSCT

Background: During HSCT, patients receive high dose chemotherapy during a prolonged hospitalization and endure significant side effects in the hopes of curing their disease. While many studies have focused on the long-term outcomes of patients undergoing HSCT, the acute impact of hospitalization for HSCT on patients QOL, symptom burden, and mood is unknown.

Table 1: Longitudinal QOL, Fatigue, Mood, and Mucositis by type of HSCT

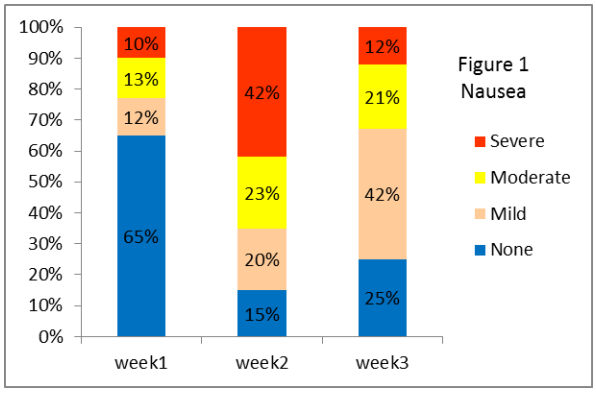
Outcome	Type HSCT	Week-1	Week-2	Week-3	P-Value
QOL, Median	Auto Allo	105.8 110.0	94.9 97.5	96.3 96.9	**p< 0.0001** **p< 0.0001**
Fatigue, Median	Auto Allo	34.4 38.5	27.0 34.3	27.3 30.9	**p< 0.0001** **p= 0.002**

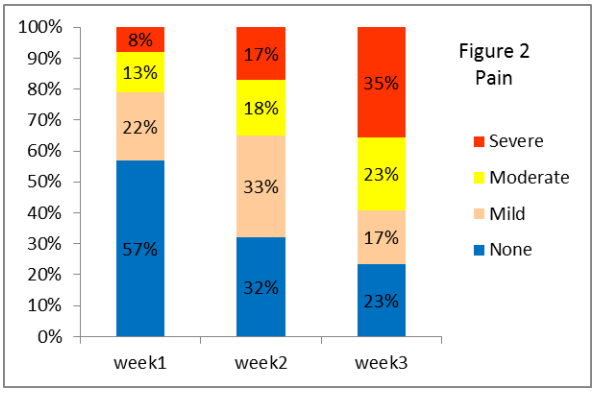
HADS Depression > 7,%	Auto Allo	23% 13%	40% 30%	43% 23%	**p= 0.002** **p= 0.03**
Mucositis, Median	Auto Allo	NA NA	8.6 18.0	19.1 23.8	**p= 0.009** **p= 0.05**

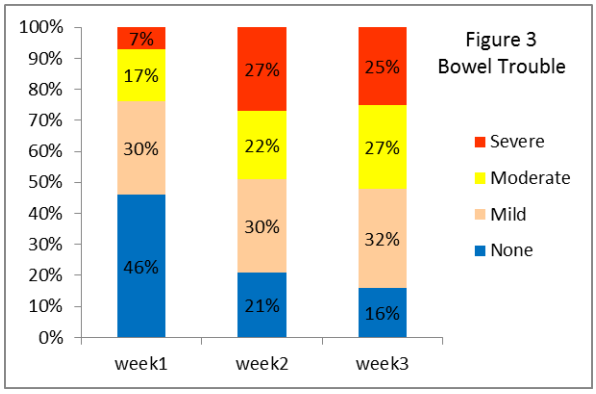
Methods: We conducted a prospective longitudinal study of patients hospitalized at the MGH for HSCT. At baseline and week 1, 2, and 3 of hospitalization, we assessed QOL (Functional Assessment of Cancer Therapy-Bone Marrow Transplantation [FACT-BMT], higher scores indicate better QOL), fatigue (FACT-Fatigue, higher scores indicate less fatigue), mucositis (Patient-Reported Oral Mucositis Scale [PROMS], higher score indicates worse mucositis symptoms) and mood (Hospital Anxiety and Depression Scale score > 7 on anxiety or depression subscale considered clinically significant). We used the SF-36 to examine family caregivers' QOL (The SF36 has two summary scores: Physical Component Scale [PCS] and Mental Component Scale [MCS]). We examined the trend of physical symptoms (nausea, pain, sleep disturbances, and bowel trouble) over time using specific items from the FACT-BMT.

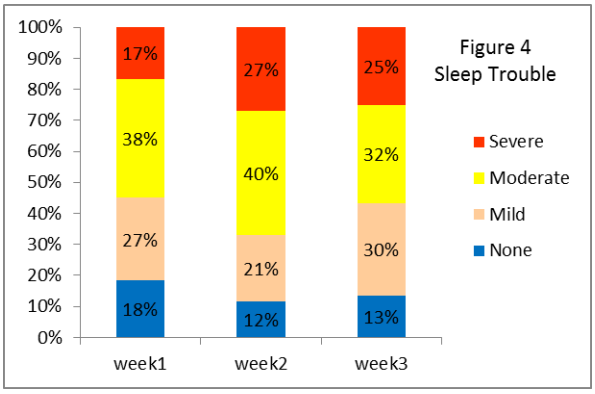
Results: We enrolled 98% (60/61) consecutive eligible patients undergoing autologous (n=30), or myeloablative allogeneic (n=30) HSCT. Patients' QOL declined and fatigue and mucositis severity increased throughout hospitalization [Table 1]. The proportion of patients with depression symptoms increased from baseline to week 3 (18.3% to 33.3%, p=0.002) whereas the proportion of patients with anxiety symptoms did not change significantly from baseline (22.6%, p=0.7). Rates of nausea were highest at week-2 of hospitalization with 65% of participants experiencing moderate to severe nausea [Figure 1]. At week-3, 58% of participants reported moderate or severe pain [Figure 2] and 53% reported moderate to severe bowel troubles [Figure 3]. Patients reported moderate to severe sleep disturbances throughout hospitalization with the highest severity at week-2 [Figure 4]. These patterns remained consistent when data were stratified by type of HSCT. While family caregivers had similar PCS scores during the patient's hospitalization, their MCS scores declined over time.

Conclusions: Patients with hematologic malignancies undergoing HSCT experience significant decline in QOL with increasing symptom burden and rates of depression throughout their hospitalization. Family caregivers also experience increasing psychological distress. Results suggest that interventions to both improve the QOL and psychological outcomes of patients hospitalized for HSCT and their family caregivers are warranted.









2 Objectives

Objective 1: To determine the impact of an inpatient palliative care intervention on patient-reported QOL during hospitalization for HSCT

Hypothesis: Patients randomized to the palliative care intervention will report improved QOL during hospitalization compared to patients receiving standard transplant care.

Objective 2: To examine the impact of an inpatient palliative care intervention on patient-reported physical and psychological symptoms during hospitalization for HSCT.

Hypothesis: Patients randomized to the palliative care intervention will report lower physical and psychological symptoms compared to patients receiving standard transplant care.

Objective 3: To assess the effect of an inpatient palliative care intervention on patients' long term QOL and psychological symptoms.

Hypothesis: Compared to patients receiving standard transplant care, patients randomized to the intervention will report improved QOL and lower depressive and post-traumatic stress symptoms at 3 and 6 months post-HSCT.

Objective 4: To examine the impact of an inpatient palliative care intervention on family-caregiver reported QOL and psychological symptoms during the patients' hospitalization for HSCT.

Hypothesis: Compared to family caregivers of patients receiving standard transplant care, caregivers of patients randomized to the intervention will report higher QOL and lower psychological symptoms during the patients' hospitalization for HSCT.

Exploratory Objective 1: To assess the impact of an inpatient palliative care intervention on non-relapse mortality (NRM), and overall survival (OS).

Exploratory Objective 2: To examine the effect of an inpatient palliative care intervention on the incidence of acute graft-versus-host disease (GVHD) and chronic GVHD.

Qualitative Objective 1: To explore patients' and palliative care clinicians' perception of the palliative care intervention, its efficacy, and any additional concerns or symptoms that have not been adequately addressed with the current intervention.

3 Research Subject Selection

3.1 Study Subject Selection:

We will recruit 160 consecutive adult patients with hematologic malignancies admitted for HSCT at Massachusetts General Hospital (MGH). We will recruit patients within 72 hours of admission to the transplant unit. We will ask patients interested in participating in the study to identify a caregiver (e.g., a relative or friend) upon whom they rely for help. We will invite this person to participate in the family caregiver portion of the study. Patients without a willing or available family caregiver will still be eligible to participate in the study. A maximum of 160 family caregivers will participate in this study.

Patients Eligibility Criteria:

1) Adult patients (≥18 years) with hematologic malignancy admitted to MGH HSCT are eligible for the study.
2) Ability to speak English or able to complete questionnaires with minimal assistance required from an interpreter or family member.

Patients Exclusion Criteria:

1) Patients with prior history of HSCT.
2) Patients undergoing HSCT for a benign hematologic condition (myelodysplastic syndrome (MDS) is not considered a benign hematologic condition and patients with MDS are eligible for the study)
3) Significant uncontrolled psychiatric disorder (psychotic disorder, bipolar disorder, major depression) or other co-morbid disease (dementia, cognitive impairment), which the treating clinician believes prohibits informed consent or participation in the study.
4) Patients enrolled on other supportive care intervention trials.

Caregivers Eligibility Criteria:

1) Adult caregivers (>18 years) of patients undergoing HSCT at MGH who agreed to participate in study.
2) A relative or a friend, identified by the patient who either lives with the patient or has in-person contact with him or her at least twice per week.
3) Ability to read questions in English or willing to complete questionnaires with the assistance of an interpreter.

4 Research Subject Entry

4.1 Study Research Subject Entry

A total of 160 patients with hematologic malignancies undergoing autologous or allogeneic HSCT will participate in this study. At MGH, there is a pre-transplant list that is updated with all potential upcoming transplant candidates. The pre-transplant list is circulated and discussed during the weekly transplant meeting with all transplant clinicians. All MGH transplant oncologists have agreed to have their eligible patients approached by research staff for participation in the study. The research staff will identify potential participants by accessing the pre-transplant list for all upcoming HSCT scheduled at MGH. Once an eligible patient is identified, the research staff will inform the attending physician that the patient and their family caregivers will be approached to participate in the study and to inquire about any concerns regarding their study participation. If the oncologists have objections to their patients' participation in the study, we will document the reason and not approach those individuals. Similarly, if

the oncologist believes the patient is appropriate for study participation but have concerns regarding the family caregiver, we will document these concerns and only approach the patient for study enrollment.

If the oncologist has no concerns regarding the patient's participation, the research staff will approach eligible patients within 72 hours of admission to the transplant unit for their HSCT. The research assistant (RA) 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 RA will obtain written informed consent from participants and provide them with a copy of the signed consent form. In addition, family caregivers will be eligible to enroll either at the same time as their loved one or within 72 hours after the patient provides written informed consent. If the family caregiver is unavailable in person, we will contact them over the phone to request study participation. The RA will contact the family caregivers via telephone a maximum of two times during this period. The RA will briefly review the study purpose and procedures over the telephone and describe the timing of administration for the questionnaires with family caregivers who are considering participation. Willing family caregiver participants not available in person will provide verbal informed consent over the telephone in order to minimize the burden of the study to the caregivers and ensure that they are able to participate in the study within the time window allowed for their enrollment.

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 admission to the transplant unit. Patients who sign informed consent and complete baseline questionnaires are then registered with QACT and randomized to palliative care intervention vs. standard transplant oncology care. If patients sign the consent, but do not complete baseline questionnaire, they will not count towards accrual numbers. Patients admitted for HCT are enrolled and registered through QACT. If the transplantation treatment is aborted due to an illness or infection, those participants will be deemed ineligible for study participation and will not be counted toward accrual. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

4.2 REGISTRATION AND RANDOMIZATION PROCEDURES

4.2.1 Patient and Caregiver Registration and Randomization

Patient and family caregivers who provide informed consent will complete baseline study measures (outlined in Selection of Instruments, section 5.2), including demographic questionnaire.

After administration of baseline questionnaires, patients (and their family caregivers) will be registered with the Quality Assurance Office for Clinical Trials (QACT) and randomized to the palliative care intervention or standard care. Randomization will be stratified by the type of HSCT (autologous/ myeloablative allogeneic/ or reduced intensity allogeneic) to ensure adequate representation of the type of HSCT in the two arms. To randomize and/or register a research subject to this protocol, contact the QACT, fax 617-632-2295.

When registering subjects through the QACT, the Center will ask the following information:

- Name and telephone number of a person contacting the QACT;
- Protocol name and number;
- Date subject begins the study;
- Subject name;
- Subject date of birth
- Service;
- Subject ID number;
- Treating physician;
- Treating institution;
- Confirmation of eligibility (Eligibility Checklist, if applicable);
- Stratification or classification factors, if applicable.

After randomization the research staff will inform the patients by phone or in person of their study arm assignment.

4.2.2 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.

4.2.3 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.

4.2.4 General Guidelines for Other Investigative Sites: Not applicable

4.2.5 Registration Process for Other Investigative Sites: Not applicable

5 Study Design and Methods

5.1 Design/ Study Type

The proposed project is a prospective randomized study evaluating the efficacy of an inpatient palliative care intervention integrated with standard transplant care compared to standard transplant care alone in 160 patients with hematologic malignancies admitted for HSCT. Randomization will be stratified by the type of HSCT (autologous/ myeloablative allogeneic/ or reduced intensity allogeneic) to ensure adequate representation of the type of HSCT in the two arms. The objectives of the study are to determine the impact of an inpatient palliative care intervention on (1) patient-reported QOL during hospitalization for HSCT (2) patient-reported physical and psychological symptoms during hospitalization for HSCT; (3) long-term (3-month and 6-month) QOL and psychological symptoms of patients undergoing HSCT; (4) family caregiver QOL and mood symptoms during the patients' hospitalization.

5.2 Study Procedures:

We will recruit 160 patient with hematologic malignancies admitted for HSCT and up to 160 family caregivers for this study. Patients will be randomized to an inpatient palliative care intervention integrated with standard transplant care compared to standard transplant care alone.

5.3 Selection of study instruments

1. ***Demographics:***

Patients and family caregivers 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].

2. ***Participant-reported measures:***

- ***QOL-Patient:*** 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 HSCT.[82] The FACT-BMT consists of four subscales assessing well-being across four domains (physical, functional, emotional, and social), as well as additional questions specific to the transplant population. These self-reported measures possess strong psychometric properties and have been validated for patients with leukemia [appendix B].

- ***Symptoms-Patient:*** We will administer the revised Edmonton Symptom Assessment Scale (ESAS) to assess various symptoms relevant to this population. The revised Edmonton Symptom Assessment Scale has been well validated and extensively studied in patients with cancer undergoing active chemotherapy treatment [Appendix C][83].

- ***Symptoms-Fatigue***: The FACT-Fatigue subscale consists of 13-items specific to fatigue symptoms, which has been used in this patient population [appendix D].[84]

- ***QOL-Family caregiver:*** We will use the CareGiver Oncology QOL questionnaire (CarGOQOL) to measure family caregiver QOL. The CarGOQOL is a 29-items well-validated instrument to measure QOL in multiple domains.[85] The CarGOQOL has been previously validated for FC of patients with cancer including hematologic malignancies [Appendix E]

- ***Mood:*** We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety in all study participants (patients and FC). The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week [appendix F] [86]. Used extensively in samples of patients with cancer and their caregivers, the questionnaire consists of a four-point item response form that quantifies the degree to which participants experience mood symptoms. Scores on each subscale range from 0 to 21, with a cutoff of 8 or greater denoting clinically significant anxiety or depression. We will also use the PHQ-9 to assess major depressive syndrome in study participants. The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the diagnostic and statistical manual of mental disorders-IV [appendix G] [87].

- ***Distress:*** We will use the NCCN Distress Thermometer and Problem Checklist to measure patients' distress and identify practical, family, emotional, spiritual, and/or physical problems causing distress.[88] The NCCN Distress Thermometer and Problem Checklist is a well-validated measure of patients' distress that has been used in patients with cancer including those with hematologic malignancies [appendix H].

- ***PTSD:*** **Post-Traumatic Stress Disorder:** We will use the Post-Traumatic Stress Disorder Checklist (PCL) to assess symptoms of post-traumatic stress in patients at baseline and six months post transplantation. The PCL is a 17 item self-reported measure that evaluates symptoms of post-traumatic stress disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV [Appendix I]. [51]

3. **Qualitative Data Collection:** We will also conduct qualitative interviews with the first five patients randomized to the palliative care intervention. The purpose of the qualitative interviews is to discuss in depth the experience of patients randomized to the intervention arm, their perception of its efficacy, and their thoughts regarding additional challenges and/or symptoms that were not adequately addressed during their hospitalization [Appendix J]. We will also conduct qualitative interviews with the palliative care clinicians administering the intervention to explore their perceptions regarding the time and effort needed to implement the intervention, and any additional thoughts and/or concerns with respect to improving the care for this population [Appendix K]. Palliative care clinicians participating in the qualitative study will sign written informed consent.

4. **Exploratory Objective Data Collection:** We will collect the following outcomes of interest from the electronic medical record:

    - 1 year overall survival: defined as death from any cause.
    - 1 year non-relapse mortality (NRM): defined as time to death occurring in continuous complete remission, partial response, minimal response, or stable disease.
    - Acute GVHD: defined as the occurrence of grade II to IV acute GVHD at 100 days. Death and relapse will be considered competing events.
    - Chronic GVHD: defined as the occurrence of chronic GVHD at one year. Death and relapse will be considered as competing risks.

5.4 Administration and timing of self-reported measures:

We will collect and enter all patient and family caregiver-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 during hospitalization or 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. Participating family caregivers who are not present in the hospital during the period of data collection will be provided with remote access to the REDCap system or paper-based questionnaires for home administration. The RA will contact patients (in person), and caregivers (in person or via telephone) daily for two days to remind them to complete and return the surveys. If study participants fail to complete the surveys within two days of the expected time point, we will report the data as missing and document the reason for incompletion. Table 2 details the schedule for administering the self-report measures. All participants (patients and family caregivers) will complete baseline evaluation within 72 hours of study enrollment. All participants will then have a second evaluation during their second week of hospitalization for HSCT. Patients undergoing autologous HSCT (and their family caregivers will have their second evaluation during the hospitalization on day +5 (48 hour window: day +5 to day +7). Patients undergoing reduced intensity allogeneic HSCT (and their family caregivers) will have their second evaluation during the hospitalization on day +8 (48 hour window: day +8 to day +10). Patients undergoing myeloablative allogeneic HSCT (and their family caregivers) will have their second evaluation during the hospitalization on day +8 (72 hour window: day +8 to day +11). We have chosen these time points carefully to assess patients during their hospitalization at the peak of severity in symptoms based on the type of transplant being performed. All patients will also complete additional questionnaires at 3 and 6 months post-transplantation.

Table 2: Administration of Self-Report Measures

Participant	**Baseline**	**Week-2:(Day+5 auto, day +8 reduced intensity allo/ablative allo)**	**3 & 6-month**
Patient Measures:			
Demographics	X		
FACT-BMT/Fatigue	X	X	X
ESAS	X	X	X
HADS	X	X	X
PHQ-9	X	X	X
NCCN Distress Thermometer (Distress)	X	X	X
PCL (PTSD)	X		X
Family Caregiver Measures:			
Demographics	X		
CarGOQOL (QOL)	X	X	
HADS	X	X	
PHQ-9	X	X	

5.5 Description of Intervention

Patients randomized to the intervention will meet with palliative clinicians within 72 hours after study randomization. After the initial visit, the palliative care team will follow the patients longitudinally during

their hospitalization and will see them at least two times per week on the inpatient transplant unit. Patients, family caregivers, or the palliative care team may initiate additional visits as needed.

The palliative care team at MGH consists of board-certified physicians, advanced practice nurses, chaplains, and social workers. For this trial, physicians or advanced practice nurses will conduct all study visits. We initially conducted a systematic review of the current literature on supportive care in patients receiving high dose chemotherapy and those undergoing HSCT to ensure up-to-date and evidence-based practice implementation in the intervention design. Based on the findings of our preliminary data, we also conducted one-on-one interviews with three palliative care clinicians to design a symptom-based intervention targeting the symptomatic burden experienced by patients hospitalized for HSCT. We utilized the preliminary results of our pilot study and the findings of the systemic review to lay a foundation with the guidance of our palliative care clinicians in designing an inpatient palliative care intervention specifically targeted for this patient population.

The palliative care intervention will focus on the following symptoms outlined in our preliminary study: (1) nausea; (2) pain and mucositis; (3) fatigue; (4) sleep disturbances; (5) constipation; and (6) depression. The palliative care intervention will include the following components:

Nausea:

- Determine the severity of the nausea, type of nausea (acute, delayed, anticipatory), and review the agents used to treat patients' symptoms.
- Optimize pharmacological therapy with the combination of steroids and 5-HT3 receptor antagonists in patients with acute and delayed nausea.
- In patients with more resistant nausea, second generation 5-HT3 receptor antagonist, and/or NK-1 receptor antagonists in combination with steroids can be used.
- Consider the use of other anti-emetics such as atypical antipsychotics, metoclopramide, and compazine.
- Utilize benzodiazepines for the treatment of anticipatory nausea.

Pain and mucositis:

- Conduct a thorough assessment of the grade of mucositis, intensity of symptoms, prior use of analgesics, and potential exacerbating factors such as candidal or herpes infection.
- All patients will likely be on mucosal coating agents with topical analgesia such as magic mouth wash (maalox, diphenhydramine, viscous lidocaine) used every 4 hours.
- Topical morphine sulfate solution can also be used.
- Early implementation of morphine (or hydromorphone for those unable to take morphine) patient-controlled analgesia in patients with severe mucositis and those not responding to oral narcotic therapy.
- Assess with the transplant team the need for total parental nutrition in patients with severe symptoms.

Fatigue:

- Screen for and conduct a comprehensive clinical assessment of fatigue and explore potential causes.
- Ensure factors contributing to fatigue burden such as anemia, uncontrolled physical symptoms, sleep disturbances, inadequate nutrition are actively addressed by the transplant team.
- Normalize fatigue and promote adaptation and adjustment through non-pharmacological interventions:
    - Set realistic goals and planning activities around energy level

  - Encourage physical activity under the direct supervision of physical therapy given extreme thrombocytopenia during count nadir.
  - Teach and promote stress management and relaxation training.
- Utilize pharmacological interventions with psychostimulants in patients with moderate to severe fatigue.

Sleep disturbances:
- Assess sleep disturbances pattern, the duration of insomnia, and the potentially contributing factors (environment, physical and psychological symptoms).
- Work with the transplant team and nursing staff to address any modifiable environmental factors that could help reduce night-time sleep disruptions.
- Institute behavioral therapies for insomnia:
  - Ensure appropriate sleep hygiene such as avoiding caffeinated beverages at night, adjusting bedroom environment to decrease stimuli, and avoiding daytime naps.
  - Teach relaxation therapy such as progressive muscle relaxation, or mindful meditation.
- Utilize pharmacologic interventions such as benzodiazepine receptor agonists, anti-depressants, and atypical antipsychotics. Benzodiazepines should generally be avoided given high risk of cognitive impairment, and delirium in this population except for highly selective patients.

Constipation:
- Assess the clinical history, prior constipation history, medications used, fluid and fiber intake.
- Assess the need for hydration and promote higher fiber intake when appropriate.
- Use pharmacological interventions including stimulants, osmotic agents, synthetic disaccharide, and/or saline laxatives. Due to neutropenia, we will avoid the use of suppositories, enemas, and manual disimpaction.

Diarrhea:
- Review the clinical history, duration and severity of diarrhea, the timing, and potential etiologies (infectious, chemo-induced, GVHD, other)
- Work with the transplant team to ensure appropriate infectious work-up, and adequate hydration.
- In patients with chemotherapy induced diarrhea, use agents such as loperamide and lomotil. Octreotide can also be used for patients with diarrhea resistant to standard therapy.
- In patients with acute GVHD, the transplant team will be responsible for the management of systemic therapy. The palliative care team can recommend the use of non-absorbable steroids.

Depression:
- Screen for depression and distinguish it from other physical symptoms experienced.
- Provide supportive psychotherapy and involve social work for further supportive therapy in patients with mild depression
- Initiate antidepressants for the treatment of moderate to severe depressive symptoms
- Assess for suicidal ideations and for more complex psychiatric management, consult psychiatry.

5.6 Standard of care (non-intervention) arm:

Patients randomized to the standard care arm will not meet with palliative care clinicians, though they may consult with palliative care at their request or at the discretion of their treating oncologist. In the transplant unit at MGH, palliative care is consulted in less than 5% of patients admitted for HSCT, and therefore we anticipate minimal cross contamination in this study.

5.7 Data Collection

As discussion previously in section 5.5 (Administration and timing of self-reported measures), we will collect and enter all patient and family caregiver-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.

5.8 Description of Study Process

5.8.1 Study Instrument Administration

Patients and FC will use tablet computers to complete baseline and longitudinal questionnaires during hospitalization or in clinic (for the 3-month and 6-month timepoints). If participants refuse or are unable to complete the questionnaires on the computer, they will be permitted to use paper versions. Participating FC 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 RA will contact patients (in person), and caregivers (in person or via telephone) daily for two days to remind them to complete and return the surveys. If study participants fail to complete the surveys within two days of the expected time point, we will report the data as missing and document the reason for incompletion.

5.8.2 Intervention Administration

Patients randomized to the palliative care intervention will meet with palliative clinicians within 72 hours after study randomization during their hospitalization for HSCT. After the initial visit, the palliative care team will follow the patients longitudinally during their hospitalization and will see them at least two times per week on the inpatient transplant unit. Patients, family caregivers, or the palliative care team may initiate additional visits as needed. Patients, family caregivers, or the palliative care team may elect to follow patients in the outpatient palliative care clinic after discharge from the hospital. However, this will not be mandated by the intervention.

Participants receiving standard transplant care will not meet routinely with the palliative care clinicians, though they may consult with palliative care at their request or the discretion of their treating oncologists. Thereafter, individual palliative care clinicians may follow standard transplant care participants per their clinical judgment, rather than according to the required twice weekly visits during the hospitalization for HSCT for study patients randomized to the inpatient palliative care intervention.

5.8.3 Special Concerns

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

5.8.4 Compensation

We will provide no patient, family caregiver or clinician compensation for participating in this study.

5.9 Adverse Reactions and Their Management

5.9.1 Reporting Adverse or Unanticipated Events

This study is evaluating the efficacy of a symptom-based intervention with minimal chance of causing harm. We have administered all of the questionnaires to over 100 patients and family caregivers 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.

5.9.2 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 (patient or caregiver) 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 and/or the hospital.

5.9.3 Reaction Management

Should participants (patient or caregiver) experience distress; the inpatient or outpatient transplant social worker will be contacted to see the participant. All inpatient and outpatient 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 (patient or caregiver) 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 and family caregiver 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 is comparison of the change in patients' FACT-BMT score from baseline to week-2 (day+5 for autologous, or day +8 for myeloablative or reduced intensity allogeneic HSCT) between study arms.

7.1.2 Secondary endpoint:

1. Compare change in patients' FACT-BMT score from baseline to 3-months and baseline to 6-months between study arms.
2. Compare rates of patients' depressive symptoms (as per HADS), major depressive syndrome (as per PHQ-9), and distress (as per NCCN Distress Thermometer) at baseline, week-2 of hospitalization (day+5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT), 3 months, and 6 months between study arms.
3. Compare change in patients' fatigue scores (as per FACT-Fatigue) from baseline to week-2 (day+5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT), baseline to 3 months, and baseline to 6 months between study arms.
4. Compare symptom burden (as per ESAS) at baseline, week-2 of hospitalization (day+5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT), 3 months, and 6-months between study arms.
5. Compare rates of patient-reported PTSD (as per PCL) at 3 and 6 months between study arms.
6. Compare change in family caregiver quality of life (as per CaGOQOL) from baseline to week-2 (day+5 for autologous, day + 8 for myeloablative or reduced intensity allogeneic HSCT) between study arms.
7. Compare rates of family caregivers' depressive symptoms (as per HADS) and major depressive syndrome (as per PHQ-9) at week-2 of hospitalization (day+5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT) between study arms.
8. Compare OS and NRM at one year between study arms.
9. Compare the cumulative incidence of acute GVHD at 100 days and chronic GVHD at one year between the study arms.
10. To explore patients' and palliative care clinicians' perception of the palliative care intervention, its efficacy, and any additional concerns or symptoms that have not been adequately addressed with the current intervention.

7.2 ***Sample Size Calculation:***

The primary endpoint of the study is a comparison of the change in FACT-BMT score during hospitalization from baseline to day +5 for autologous HSCT, or day +8 for myeloablative or reduced intensity allogeneic HSCT between study arms. A 5-point change in FACT-BMT QOL score is considered clinically meaningful. In our prior randomized study in patients with metastatic lung cancer, we noted a 6.5 point change in QOL between the intervention and control group.[79] Given the extent of QOL deterioration seen in the transplant population in our pilot study, a 6.0 point change in QOL between the two study arms should be a conservative estimate of the likely effect of our intervention. Enrolling 64 patients per arm will provide 80% power to detect at least a 6.0 point change from baseline to week 2 between arms using a two-sample t-test with a 0.05 significance level. Based on our pilot experience, we estimate the rate of attrition and missing data to be 15%. We will increase our sample size to 80 patients per arm to ensure a sufficiently large margin to have adequate power to detect clinically meaningful differences in QOL between the study groups

Patients who consent for the study, but do not complete baseline questionnaires will not be registered or randomized and therefore will not count towards accrual numbers and will be replaced by eligible participants who consent and complete baseline questionnaires. Patients admitted for HCT are enrolled and registered through QACT. If the transplantation treatment is aborted due to an illness or infection, those participants will be deemed ineligible for study participation and will not be counted toward accrual. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

*7.3 **Stratification factors and intervention allocation plan for randomized studies:***

Patients will be randomized in a 1:1 fashion between study arms with stratification only for the type of transplant (autologous/reduced intensity allogeneic/ myeloablative allogeneic). After randomization, research staff will inform patients by phone or in person of their study assignments.

*7.4 **Definition of an allowance in design for unevaluable/ineligible participants:***

Only patients who do not complete the baseline data collection will be considered unevaluable and they will not count towards accrual numbers. All participants who complete baseline data collection will be included and analyzed regardless of whether they comply with the intervention or longitudinal data collection (intention to treat analysis). Our primary endpoint is change in patient-reported quality of life from baseline to week-2 of hospitalization (day +5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT). The required sample size to detect a 6.0 point change is 128 patients. However, based on our pilot experience, we estimate attrition and missing data rate to be 15%. Therefore, we have increased our sample size to 80 patients per arm (160 total) to ensure a sufficiently large margin to have adequate power to detect clinically meaningful differences in QOL between the study groups.

*7.5 **Analysis Plan:***

Objective 1: To determine the impact of an inpatient palliative care intervention on patient-reported QOL during hospitalization for HSCT

This is the primary endpoint of this study. We will compare changes in QOL (FACT-BMT) scores from baseline to week-2 (day+5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT) between the study arms using the two-sample t-test.

Objective 2: To examine the impact of an inpatient palliative care intervention on patient-reported physical and psychological symptoms during hospitalization for HSCT.

We will compare changes in symptoms (ESAS) and fatigue (FACT-Fatigue) from baseline to week-2 (day +5 for autologous, day + 10 for myeloablative or reduced intensity allogeneic HSCT) between the study arms using the two-sample t-test or the Wilcoxon rank sum test based on the normality of the data.

We will also compare the rate of psychological distress between study arms during the second week of hospitalization (day +5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT). We will transform the HADS score into a dichotomous outcome with categories reflecting the presence or absence of clinically significant depression and anxiety. We will then calculate Fisher's exact tests to assess the association between study arm and the presence of depression/anxiety, using risk difference and relative risk to compare proportions between the two groups. We will similarly dichotomize the PHQ-9 scores (to reflect the presence or absence of depression), and the Distress Thermometer score (to reflect the presence or absence of distress) and analyze the data using the Fisher's exact test. We will use either the two-sample t-test or the Wilcoxon signed rank test, as appropriate to the univariate distribution of the raw scores, to compare the problem checklist scores between groups for each time point.

Objective 3: To assess the effect of an inpatient palliative care intervention on patients' long term QOL and psychological symptoms.

We will compare change in FACT-BMT scores from baseline to 3-months, and from baseline to 6-months between the two arms using the two-sample t-test. We will compare the rate of patients' psychological distress between study arms at 3-months and 6-months by analyzing HADS, PHQ-9, and NCCN Distress Thermometer and checklist scores as outlined in the statistical plan for objective-2. We will compare PTSD scores (PCL) at 3-months and 6-months between study arms using either two sample t-test or Wilcoxon rank sum test as appropriate for the data.

Mixed linear models will be fitted to adjust for selected demographic and clinical factors when examining change in QOL and fatigue scores across all time points (baseline, week-2, 3 months, and 6 months).

Objective 4: To examine the impact of an inpatient palliative care intervention on family-caregiver reported QOL and psychological symptoms during the patients' hospitalization for HSCT.

We will compare change in family caregivers' QOL (CarGOQOL) from baseline to week-2 (day +5 for autologous, day +8 for myeloablative or reduced intensity allogeneic HSCT) between the study groups using the two-sample t-test. We will also compare the rate of family caregivers' psychological distress (HADS, PHQ9) between study arms at week 2 of hospitalization as outlined in the statistical plan for objective-2.

Exploratory Objectives: We will assess OS, NRM, cumulative incidence of acute GVHD, and cumulative incidence of chronic GVHD using Kaplan-Meier estimates, testing the difference between the curves with the Log-Rank test. We will analyze NRM using a competing risk analysis. The proportion between the study arms will be compared by the chi-square test or Fisher's exact test.

Qualitative objective: We will analyze data obtained from qualitative interviews with first 5 patients randomized to the palliative care intervention and the palliative care clinicians administering the intervention using content analysis. The analyses will entail a multi-step process to explore 1) patients' perception of the palliative care intervention and its efficacy; 2) palliative care clinicians' perception of the palliative care intervention and its administration; 3) patients' perception of additional concerns and/or symptoms that have not been adequately addressed with the intervention; 4) palliative care clinician's perception of the unmet needs of this population. We will analyze the qualitative interviews 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. The analyses will involve coding to structure data into categories and creating groups according to broader issues or themes. Major and minor theses within each content area will be identified and messages will be extracted and highlighted. To ensure reliability and to check for validity, two study investigators will conduct the coding separately. Coders will examine discrepant, unexpected, or unclear data until agreement is reached. To assure the trustworthiness of our findings, steps will be taken to maximize reliability and credibility including: investigator triangulation (using a multidisciplinary team of investigators), and team debriefs of the interview content.

7.6 ***Handling of Missing Data:***

We will explore imputation methods like multiple imputation and last observation carried forward favoring the more conservative method in handling missing data.

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Supplement B

Palliative Care Intervention Manual

Patients randomized to the intervention will meet with palliative clinicians within 72 hours after study randomization. After the initial visit, the palliative care team will follow the patients longitudinally during their hospitalization and will see them at least two times per week on the inpatient transplant unit. Patients, family caregivers, or the palliative care team may initiate additional visits as needed.

The palliative care team at MGH consists of board-certified physicians, advanced practice nurses, chaplains, and social workers. For this trial, physicians or advanced practice nurses will conduct all study visits. We initially conducted a systematic review of the current literature on supportive care in patients receiving high dose chemotherapy and those undergoing HCT to ensure up-to-date and evidence-based practice implementation in the intervention design. Based on the findings of our preliminary data, we also conducted one-on-one interviews with three palliative care clinicians to design a symptom-based intervention targeting the symptomatic burden experienced by patients hospitalized for HCT. We utilized the preliminary results of our pilot study and the findings of the systemic review to lay a foundation with the guidance of our palliative care clinicians in designing an inpatient palliative care intervention specifically targeted for this patient population.

The palliative care intervention will focus on the following symptoms outlined in our preliminary study: (1) nausea; (2) pain and mucositis; (3) fatigue; (4) sleep disturbances; (5) constipation; and (6) depression. The palliative care intervention will include the following components:

Nausea:

- Determine the severity of the nausea, type of nausea (acute, delayed, anticipatory), and review the agents used to treat patients' symptoms.
- Optimize pharmacological therapy with the combination of steroids and 5-HT3 receptor antagonists in patients with acute and delayed nausea.
- In patients with more resistant nausea, second generation 5-HT3 receptor antagonist, and/or NK-1 receptor antagonists in combination with steroids can be used.
- Consider the use of other anti-emetics such as atypical antipsychotics, metoclopramide, and compazine.
- Utilize benzodiazepines for the treatment of anticipatory nausea.

Pain and mucositis:

- Conduct a thorough assessment of the grade of mucositis, intensity of symptoms, prior use of analgesics, and potential exacerbating factors such as candidal or herpes infection.
- All patients will likely be on mucosal coating agents with topical analgesia such as magic mouth wash (maalox, diphenhydramine, viscous lidocaine) used every 4 hours.
- Topical morphine sulfate solution can also be used.
- Early implementation of morphine (or hydromorphone for those unable to take morphine) patient-controlled analgesia in patients with severe mucositis and those not responding to oral narcotic therapy.
- Assess with the transplant team the need for total parental nutrition in patients with severe symptoms.

Fatigue:

- Screen for and conduct a comprehensive clinical assessment of fatigue and explore potential causes.
- Ensure factors contributing to fatigue burden such as anemia, uncontrolled physical symptoms, sleep disturbances, inadequate nutrition are actively addressed by the transplant team.
- Normalize fatigue and promote adaptation and adjustment through non-pharmacological interventions:
    - Set realistic goals and planning activities around energy level

    - Encourage physical activity under the direct supervision of physical therapy given extreme thrombocytopenia during count nadir.
    - Teach and promote stress management and relaxation training.
- Utilize pharmacological interventions with psychostimulants in patients with moderate to severe fatigue.

Sleep disturbances:

- Assess sleep disturbances pattern, the duration of insomnia, and the potentially contributing factors (environment, physical and psychological symptoms).
- Work with the transplant team and nursing staff to address any modifiable environmental factors that could help reduce night-time sleep disruptions.
- Institute behavioral therapies for insomnia:
    - Ensure appropriate sleep hygiene such as avoiding caffeinated beverages at night, adjusting bedroom environment to decrease stimuli, and avoiding daytime naps.
    - Teach relaxation therapy such as progressive muscle relaxation, or mindful meditation.
- Utilize pharmacologic interventions such as benzodiazepine receptor agonists, anti-depressants, and atypical antipsychotics. Benzodiazepines should generally be avoided given high risk of cognitive impairment, and delirium in this population except for highly selective patients.

Constipation:

- Assess the clinical history, prior constipation history, medications used, fluid and fiber intake.
- Assess the need for hydration and promote higher fiber intake when appropriate.
- Use pharmacological interventions including stimulants, osmotic agents, synthetic disaccharide, and/or saline laxatives. Due to neutropenia, we will avoid the use of suppositories, enemas, and manual disimpaction.

Diarrhea:

- Review the clinical history, duration and severity of diarrhea, the timing, and potential etiologies (infectious, chemo-induced, GVHD, other)
- Work with the transplant team to ensure appropriate infectious work-up, and adequate hydration.
- In patients with chemotherapy induced diarrhea, use agents such as loperamide and lomotil. Octreotide can also be used for patients with diarrhea resistant to standard therapy.
- In patients with acute GVHD, the transplant team will be responsible for the management of systemic therapy. The palliative care team can recommend the use of non-absorbable steroids.

Depression:

- Screen for depression and distinguish it from other physical symptoms experienced.
- Provide supportive psychotherapy and involve social work for further supportive therapy in patients with mild depression
- Initiate antidepressants for the treatment of moderate to severe depressive symptoms
- Assess for suicidal ideations and for more complex psychiatric management, consult psychiatry.

Supplementary Tables

Supplemental Table 1: Mixed linear effect models of patient-reported outcomes using multiple imputations: ǂ analyses are adjusted for baseline outcome scores

Week-2 outcomes (N=160)	Adjusted Betaǂ	95% Confidence Interval	P- Value
FACT-BMT	7.57	1.18 to 13.96	**0.020**
FACT- Fatigue	3.77	0.09 to 7.44	**0.045**
HADS-D depression symptoms	-1.71	-2.97 to -0.45	**0.008**
HADS-A anxiety symptoms	-2.24	-3.19 to -1.29	**<0.001**
PHQ-9 depressive symptoms	-1.23	-2.75 to 0.30	0.116
ESAS – Symptom burden	-7.34	-12.51 to -2.17	**0.005**
3 months outcomes (N=160)	**Adjusted Betaǂ**	**95% Confidence Interval**	**P-Value**
FACT-BMT	5.31	-0.10 to 10.72	0.055
FACT- Fatigue	1.82	-1.27 to 4.91	0.249
HADS-D depression symptoms	-1.64	-2.70 to -0.59	**0.002**
HADS-A anxiety symptoms	-0.71	-1.68 to 0.25	0.148
PHQ-9 depressive symptoms	-2.06	-3.33 to -0.78	**0.002**
ESAS – Symptom burden	-2.59	-6.49 to 1.31	0.193
PTSD	-4.05	-6.81 to -1.30	**0.004**

Supplemental Table 2: Mixed linear effect models of family caregiver-reported outcomes using multiple imputations: ǂ analyses are adjusted for baseline outcome scores

Week-2 outcomes (N = 94)	Adjusted Betaǂ	95% Confidence Interval	P- Value
FC-QOL	3.66	-1.28 to 8.61	0.146
Psych	0.60	-0.62 to 1.82	0.334
Burden	0.68	-0.41 to 1.77	0.219
Relationship health care	-0.25	-1.08 to 0.57	0.552
Administrative and finances	0.72	0.10 to 1.35	**0.024**
Coping	0.97	0.15 to 1.79	**0.021**
Physical	0.50	-0.56 to 1.56	0.357
Self-esteem	**-0.18**	**-0.71 to 0.34**	0.494
Leisure	0.25	-0.38 to 0.89	0.438
Private Life	0.64	-0.09 to 1.37	0.086
Social support	-0.25	-0.83 to 0.34	0.405
FC depression	-1.79	-3.39 to -0.18	**0.029**
FC anxiety	-0.07	-1.54 to 1.41	0.926
FC PHQ	-0.29	-1.90 to 1.32	0.725