

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

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*Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies
Undergoing Hematopoietic Stem Cell Transplantation*

PRINCIPAL INVESTIGATOR:

Name: Areej El-Jawahri

Department: Hematology-Oncology

Telephone Number: 617-724-4000

Email Address: ael-jawahri@partners.org

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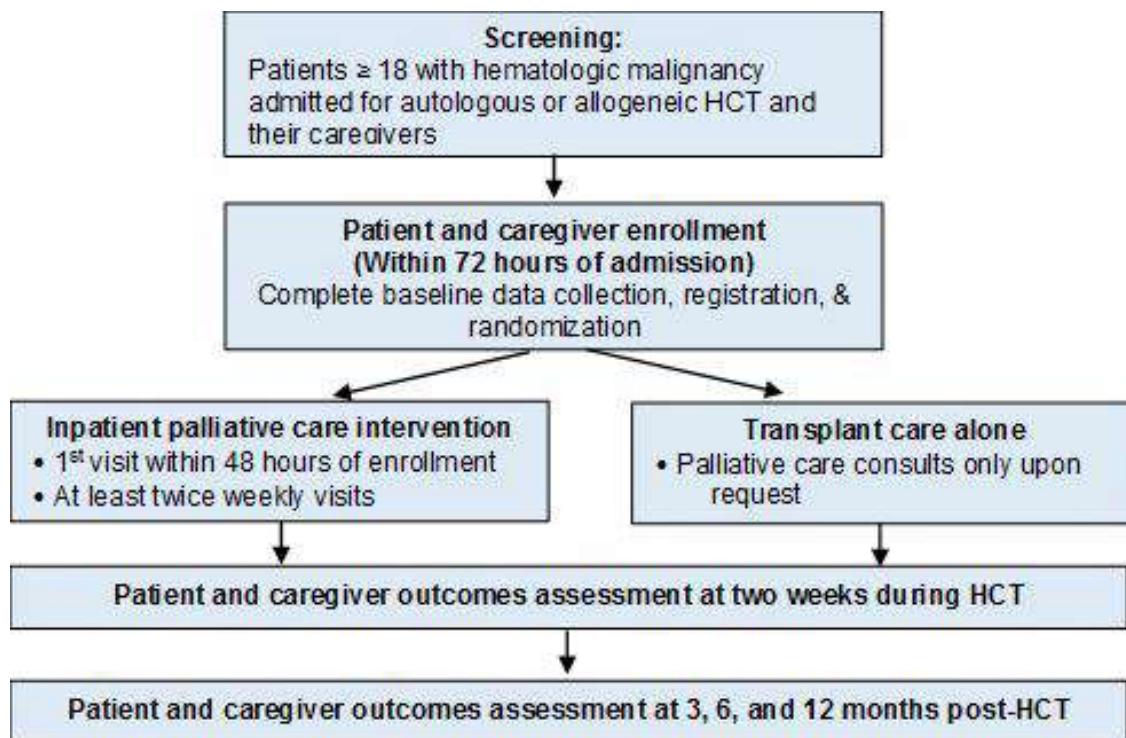
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Section 1: Protocol Schema



PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

Table of Contents

1.0	Objectives*	4
2.0	Background*	5
3.0	Inclusion and Exclusion Criteria*	7
4.0	Study-Wide Number of Subjects*	8
5.0	Study-Wide Recruitment Methods*	8
6.0	Multi-Site Research*	10
7.0	Study Timelines*	11
8.0	Study Endpoints*	12
9.0	Procedures Involved*	13
10.0	Data and Specimen Banking*	18
11.0	Data Management* and Confidentiality	20
12.0	Provisions to Monitor the Data to Ensure the Safety of Subjects*	25
13.0	Withdrawal of Subjects*	25
14.0	Risks to Subjects*	26
15.0	Potential Benefits to Subjects*	26
16.0	Vulnerable Populations*	26
17.0	Community-Based Participatory Research*	26
18.0	Sharing of Results with Subjects*	26
19.0	Setting	26
20.0	Resources Available	27
21.0	Prior Approvals	27
22.0	Recruitment Methods	29
23.0	Local Number of Subjects	29
24.0	Provisions to Protect the Privacy Interests of Subjects	29
25.0	Compensation for Research-Related Injury	29
26.0	Economic Burden to Subjects	29
27.0	Consent Process	30
28.0	Process to Document Consent in Writing	30
29.0	Drugs or Devices	30

1.0 Objectives

1.1 Overview

Hematopoietic stem cell transplantation (HCT) is a commonly used and potentially curative treatment strategy for many hematologic malignancies.¹⁻⁴ Patients undergoing HCT usually receive high-dose chemotherapy followed by stem cell transplantation during a 3-4 week hospitalization.⁴⁻⁶ During this hospitalization, patients experience substantial physical symptoms with 50-70% reporting moderate to severe nausea, vomiting, fatigue, diarrhea, mucositis, and pain.⁷⁻¹² These symptoms, along with the physical isolation patients experience during their prolonged hospitalization, contribute to a dramatic deterioration in their quality of life (QOL) and mood throughout their hospital stay.¹¹⁻¹³ Notably, 40% of patients report clinically significant depression and anxiety symptoms during HCT.^{8,9,11} Furthermore, patients' experience during their transplant often leads to physical and psychological symptoms post-transplant, further exacerbating the morbidity of the procedure.^{8,13,14} Patients' caregivers (i.e. family and friends) also endure significant psychological distress as they witness their loved one struggle with the toxicities of HCT.^{15,16} Supporting a loved one through HCT not only causes considerable disruptions in the caregiver's personal life, but also leads to marked distress due to the patient's uncertain prognosis.^{11,16-18} Thus, patients and their caregivers struggle with the challenges of HCT, which negatively impacts their QOL and mood both during and after transplant.

Despite the tremendous burden experienced by patients undergoing HCT and their caregivers, studies of interventions to improve their QOL and reduce distress are lacking.^{7,11,19-21} Involvement of specialty-trained palliative care clinicians in the care of patients with advanced solid tumors has been shown to improve patient's QOL and mood and reduce their caregiver's psychological distress.²²⁻²⁷ Consequently, the early integration of palliative and oncology care is becoming the standard of care for patients with advanced solid tumors.²⁸ However, palliative care is rarely consulted to assist in the management of patients with hematologic malignancies.²⁹⁻³¹ Misconceptions equating palliative care with end-of-life care have contributed to the lack of involvement of palliative care for patients undergoing potentially curative therapy with HCT.²⁹⁻³³ However, given their extensive training and expertise in managing complex symptoms, palliative care clinicians are ideally positioned to treat the challenging toxicities experienced by this population.

We completed a single center randomized trial of inpatient integrated palliative and transplant care versus transplant care alone in patients with hematologic malignancies undergoing HCT (see Preliminary Studies).³⁴ Palliative care clinicians followed patients throughout their transplant hospitalization and conducted a minimum of two visits per week to 1) address patients' physical and psychological symptoms; 2) manage patients' and caregivers' expectations; and 3) provide both patients and caregivers with strategies to cope with the patients' illness and health status. Patients randomized to receive palliative care had a significant improvement in their QOL, symptom burden, depression, and anxiety during their hospitalization compared to those randomized to transplant care alone. Notably, the effects of the intervention were sustained three and six months post-HCT with significant improvements in depression, and post-traumatic stress symptoms.^{34,35} Caregivers also reported improvements in their coping and depression symptoms.³⁴ This was the first trial to establish the feasibility and preliminary efficacy of integrated palliative and transplant care in improving outcomes for patients with hematologic malignancies and their caregivers.

We propose to conduct a multi-site randomized trial of inpatient palliative care integrated with transplant care versus transplant care alone in patients with hematologic malignancies undergoing HCT. The primary goal of this study is to test the efficacy of inpatient palliative care integrated with transplant

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

care in improving patient- and caregiver-reported outcomes in a multi-site trial with a larger and more diverse patient population. We will also assess the impact of palliative care on participants' long term QOL and psychological outcomes. Data from this R01 will lay the foundation for a future implementation and dissemination trial of this care model.

Specific Aims

1. To demonstrate the efficacy of inpatient integrated palliative and transplant care for improving patient-reported QOL and psychological outcomes.

Hypothesis: Patients randomized to the intervention versus transplant care alone will report improved QOL and fewer depression and anxiety symptoms during their HCT and at 3, 6, and 12 months post-HCT.

2. To assess the impact of inpatient integrated palliative and transplant care on caregiver-reported QOL and psychological outcomes.

Hypothesis: Caregivers randomized to the intervention versus transplant care alone will report improved QOL and fewer depression and anxiety symptoms during patients' HCT and at 3, 6, and 12 months post-HCT.

3. To explore mediators and moderators of the effect of the integrated palliative and transplant care intervention on patient-reported QOL.

Hypothesis: Intervention effects on patient-reported QOL will be mediated by enhanced coping and reduced symptom burden in patients, and potentially moderated by patient demographic and clinical factors.

2.0 Background

Patients undergoing HCT experience immense physical and psychological symptoms

High dose chemotherapy followed by HCT is an intensive and potentially curative treatment for many patients with hematologic malignancies.¹⁻⁴ The use of HCT has increased recently due to data demonstrating its efficacy for new disease indications and acceptable safety profile in older patients.^{4,6} The majority of transplants in the United States are performed in the inpatient setting with patients receiving chemotherapy followed by stem cell transplantation during a 3-4 week hospitalization.⁵ Patients undergoing HCT experience substantial physical symptoms due to chemotherapy-induced toxicities and early post-transplant complications.⁷⁻¹² Studies show that 50-70% of patients undergoing HCT report moderate to severe nausea, vomiting, diarrhea, pain, insomnia, and fatigue.^{9,11} These symptoms, along with the physical isolation patients experience during the prolonged hospitalization, contribute to a rapid and dramatic deterioration in QOL and mood throughout the hospital stay.¹¹⁻¹³ Notably, 40% of patients report clinically significant depression and anxiety symptoms during HCT.^{8,9,11} Therefore, patients undergoing HCT have tremendous physical and psychological needs that may benefit from intensive supportive care measures to improve QOL and care.

Patients' experiences during hospitalization lead to physical and psychological symptoms post-HCT

Patients' physical and psychological symptoms during HCT have negative consequences on their long-term well-being.^{8,13,14} Studies demonstrate that patients' physical and psychological distress during HCT predicts their psychological morbidity and risk of transplant-related complications months after hospitalization.^{13,14,36} Many HCT survivors develop depression and post-traumatic stress symptoms as a result of their transplant experience.^{8,13,14,37} The extent of decline in patients' QOL and increase in depression symptoms during hospitalization strongly predicts their QOL impairment and risk of post-traumatic stress symptoms post-HCT.³⁸ As many as 41% of survivors experience post-traumatic stress symptoms up to 10 years post HCT.³⁹⁻⁴² These psychological complications further compound the morbidity of HCT. Thus, improving patients' symptoms and QOL during hospitalization for HCT may positively impact their QOL and psychological distress post-HCT.^{35,38}

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

Caregivers are also negatively impacted by patients' hospitalization for HCT

The family and close friends ("caregivers") of patients undergoing HCT are also impacted by the patient's illness.^{15,16} Stress from supporting a loved one through HCT and coping with an uncertain prognosis negatively affects caregivers' social and psychological well-being.¹⁶ Moreover, watching a loved one struggle with side effects during HCT can be emotionally challenging for caregivers.¹¹ Supporting a loved one through HCT often causes disruptions in the caregiver's personal life, including difficulty maintaining responsibilities at home and work.¹⁶⁻¹⁸ Thus, caregivers of patients undergoing HCT experience substantial caregiving burden, which negatively impacts their QOL and mood.^{15,43}

Interventions to address patients' symptom burden during hospitalization for HCT are lacking

Despite the substantial burden experienced by patients undergoing HCT and their caregivers, few studies have been conducted to improve their experience or outcomes.^{7,11,19-21} Investigators have examined the role of exercise and brief psychosocial interventions during HCT, demonstrating mixed results on patients' physical functioning, pain, and well-being.^{19,20,44,45} While a cognitive behavioral intervention in patients 1-3 years post-HCT reduced post-traumatic stress symptoms,⁴⁶ interventions targeting patients' and caregivers' psychological distress during HCT are lacking.¹¹ Further study is needed to address the physical and psychological symptoms experienced by patients undergoing HCT and their caregivers to enhance overall QOL and care.

Palliative care is underutilized but can address the complex needs of patients undergoing HCT

The 2016 American Society of Clinical Oncology Clinical Practice Guideline Update recommended palliative care from the time of diagnosis for all patients with metastatic solid tumors and/or high symptom burden.²⁸ This recommendation is based on several trials demonstrating improvements in QOL, symptom burden, mood, coping, and care delivery at the end of life for patients with advanced solid tumors receiving early palliative care.²²⁻²⁵ While palliative care is increasingly involved in the care of patients with advanced solid tumors, they are rarely consulted for patients with hematologic malignancies.²⁹⁻³¹ In a recent survey conducted by the American Society of Blood and Marrow Transplant, over 90% of transplant physicians reported that they do not collaborate frequently with palliative care clinicians.⁴⁷ Studies show that palliative care has not been well integrated with transplant care, due in part to misperceptions equating palliative care with end-of-life care and lack of evidence supporting the role of palliative care for patients being treated with curative intent.²⁹⁻³³ However, palliative care clinicians possess the expertise to manage complex symptoms and provide support for patients and their caregivers. Additionally, palliative care can support the transplant team by addressing concerns, fears, and expectations of patients and their caregivers during HCT.⁴⁸⁻⁵⁰ Integrating palliative and transplant care has great potential to improve outcomes for patients undergoing HCT and their caregivers.

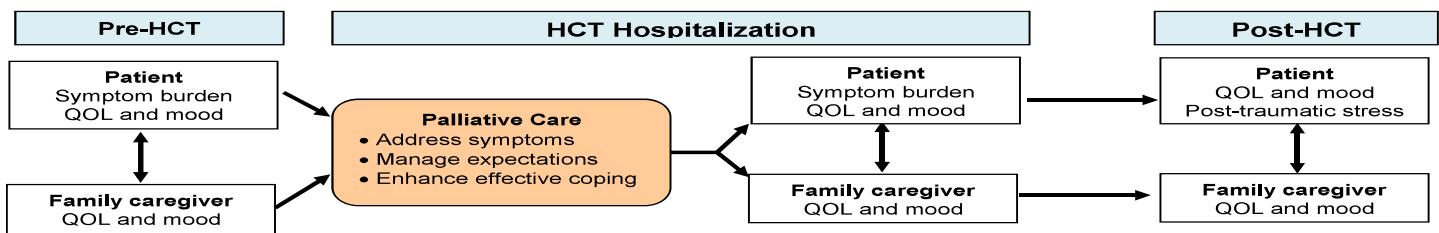
Scientific Premise of the Proposed Project: Patients with hematologic malignancies undergoing HCT struggle with immense physical and psychological symptoms that negative impact their QOL and mood and contribute to long-term morbidity.^{7-14,37} Caregivers of patients undergoing HCT also endure substantial emotional distress during and after their loved one's transplant.^{15,16} Despite the burden experienced by these individuals, few interventions have been developed to improve their QOL and care.^{7,11,19-21} We completed a single center randomized trial of inpatient palliative care integrated with transplant care versus transplant care alone in patients with hematologic malignancies undergoing HCT.³⁴ We demonstrated statistically and clinically significant improvements in patients' QOL, symptom burden, depression, and anxiety (see Preliminary Studies).⁵¹ We also found that caregivers of patients randomized to the intervention reported significant improvement in coping and depression, compared to caregivers of those receiving transplant care alone.⁵¹ Importantly, the effects of the intervention were sustained three months and six months post-HCT with patients randomized to the intervention reporting significant improvements in their depression, and post-traumatic stress symptoms compared with those receiving transplant care alone.^{35,51} This study established the feasibility and preliminary efficacy of inpatient

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation
 integrated palliative and transplant care to improve the QOL and care for patients with hematologic malignancies undergoing HCT and their caregivers.

These encouraging findings suggest that the next step in this programmatic line of research is to conduct a multi-site randomized trial to demonstrate definitively the efficacy of the intervention in improving patient- and caregiver-reported QOL and psychological distress and to establish the generalizability of the integrated care model across care settings. In addition, a large multi-site trial will enable us to explore potential mediators and moderators of the intervention effects to explore how the care model may be tailored to specific sub-populations. A 5-year study period will also allow us to assess the effects of the intervention on participants' long-term QOL and psychological outcomes. Importantly, this multi-site trial will provide the necessary data to overcome the barriers to integrating palliative care in the management of patients undergoing HCT and set the stage for future implementation and dissemination trial of this care model.

Conceptual Model: Our conceptual model in Figure 1 is adapted from a theoretical model of integrated palliative and oncology care for patients with solid tumors that is based on our team's prior research efforts.⁵² Patients' symptom burden during HCT hospitalization predicts psychological distress and QOL impairment post-HCT. The palliative care intervention will address patients' physical and psychological symptoms and both patients' and caregivers' expectations to enhance their coping during the hospitalization for HCT. Based on our prior data demonstrating changes in outcomes three and six months post-HCT, we anticipate that the intervention will lead to long-term improvements in participants' QOL and mood. As patients' symptoms and QOL during the HCT impact their caregivers' outcomes, we anticipate that the intervention will positively affect caregivers both directly by enhancing their coping and indirectly by improving patients' symptom burden and QOL.

Figure 1



3.0 Inclusion and Exclusion Criteria

We propose a multi-site randomized controlled trial of inpatient integrated palliative and transplant care versus transplant care alone in 360 patients with hematologic malignancies hospitalized for HCT and 180-360 of their caregivers. Patients will be recruited from the MGH Cancer Center, Fred Hutchinson Cancer Research Center, and Duke University. Patients will be randomized in 1:1 fashion and stratified by study site and transplant type (autologous vs. allogeneic). As autologous and allogeneic HCT have significantly different courses of recovery post-transplant,¹ we will stratify by the type of transplant to ensure adequate and balanced representation between the two study groups.

3.1 Screening Procedures:

All participating sites have an admission database which includes all planned HCT admissions. The site PIs will grant the research assistant (RA) at that site access to the database to review the weekly list of scheduled admissions for transplant to screen for eligible patients. Transplant admissions are always scheduled in advance, thus our screening method will ensure we identify all patients who are eligible for

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

study participation. We utilized these study procedures in our prior single center trial and enrolled 86% of potentially eligible participants.

3.2 Eligibility Criteria

Patient Inclusion Criteria

- 1) adult patients (≥ 18 years) with hematologic malignancy admitted for autologous or allogeneic HCT.
- 2) ability to read and respond to questions in English or Spanish or to complete questionnaires with assistance from an interpreter.

Patient Exclusion Criteria

- 1) Patients undergoing HCT for benign hematologic conditions
- 2) Patients undergoing outpatient HCT.
- 3) Patients with psychiatric or cognitive conditions which the treating clinicians believes prohibits compliance with study procedures.
- 4) Patients who already consulted Palliative Care during their HCT admission

Caregiver Eligibility Criteria:

- 1) adult (≥ 18 years) relative or a friend of a patient who agrees to participate in the study whom the patient identified as living with them or having in-person contact with him or her at least twice per week.
- 2) ability to read and respond to questions in English or Spanish or to complete questionnaires with the assistance of an interpreter.

Given the different needs of children with hematologic malignancy undergoing HCT, we will enroll patients at least 18 years of age, in approximately equal numbers of men and women who represent the cultural and demographic backgrounds of the patients seen at our participating sites. We will not include pregnant women or prisoners in this study.

4.0 Study-Wide Number of Subjects

We propose a multi-site randomized controlled trial of inpatient integrated palliative and transplant care versus transplant care alone in 360 patients with hematologic malignancies hospitalized for HCT and 180-360 of their caregivers.

5.0 Study-Wide Recruitment Methods*

5.1 Recruitment and Enrollment Procedures:

We will use the same successful recruitment and enrollment procedures from our prior single center trial. Prior to the study start, the site investigators will meet with the transplant oncology team to review recruitment and enrollment procedures. Specifically, the RA will send an email to the transplant clinicians to notify them that their patient (and caregiver) is eligible for study participation and inquire about any concerns regarding their participation [appendix J]. If the clinicians have objections to their patients' and/or caregivers' participating in the study, the RA will document the reason and not approach those individuals. If the transplant clinicians have no objections, the RA will approach patients for study participation two weeks prior to their admission date or within 72 hours of their admission for HCT (excluding public holidays, in which case the RA will approach within 96 hours). The RA will conduct informed consent procedures with potential participants and obtain written informed consent or verbal

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

consent over the telephone or a video call. Patients being contacted for verbal consent will be contacted twice a week during the two weeks prior to their transplant admission. If we are unable to contact the patient, we will leave a voicemail with our study contact information. Patients providing verbal consent will be sent an unsigned copy of the informed consent form for their records. Patients will then be asked to identify a caregiver who might be interested in participating. Patients without a willing or interested caregiver will still be eligible to participate in the study. The caregiver will be eligible to enroll in the study either at the same time as the patient or within 72 hours after the patient provides verbal or written informed consent. We will have a separate consent form for caregivers, which will similarly detail the study procedures. Caregivers will have the option of enrolling in the study in-person with a written informed consent or over the telephone with a verbal consent (Appendix N). Patients and/or caregivers who refuse study participation will be asked the reason for deferring. Study participants will complete baseline self-report assessments on the same day as providing verbal or written informed consent or within the two-week window prior to their admission date or within the 72-hour window (excluding public holidays) from admission to the transplant unit.

Patients and caregivers who speak Spanish will have all study procedures and information regarding risks, benefits and study contacts explained to them orally via the use of an interpreter as a first preference, or family member as a second preference. Spanish speaking participants will be given the DF/HCC Spanish consent short form for signing, as well as a copy of the full English consent form for their own reference. Both the Spanish consent short form, and the full English consent form will be signed by the participant, and by a witness. The witness will be either an interpreter or a family member.

***We are requesting a Waiver of Written Documentation of Consent**

This Waiver is being requested to assist with patient recruitment during the COVID-19 pandemic. Our study meets the waiver requirements given our study is considered minimal risk and all study procedures could be conveyed orally. This waiver will reduce the risk to patients and is necessary for our research procedures to continue.

***We are requesting an HIPAA Waiver of Authorization to Review Preparatory to Research from the IRB.** This Waiver is being requested to identify potential participants from a minimal chart review. In accordance with the DF/HCC policy, this Waiver: (1) is being sought solely to review Protected Health Information as necessary to prepare a research protocol, (2) will not include removing Protected Health Information from the Covered Entity by the researcher, and (3) the Protected Health Information for which we are requesting access is necessary for the research purposes.

Patients will complete baseline self-report assessments at the time of obtaining informed consent for the study or within the two-week window prior to their admission date or within the 72-hour window (excluding public holidays) from admission to the transplant unit. Patients must sign informed consent or provide verbal consent and complete the baseline questionnaire before registering with the Clinical Trials Management System. If patients consent, but do not complete baseline questionnaire, they will not count towards accrual numbers. Caregivers will have 72-hours from patient enrollment to enroll in the study and complete baseline self-reported measures. If caregivers sign the consent, but do not complete baseline questionnaire, they will not count towards the caregiver accrual numbers. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur prior to the initiation of protocol-specific procedures or assessments.

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

For registration of patients from DF/HCC institutions, study staff will complete the DF/HCC protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol and the criteria on the eligibility checklist.

Patients from other investigative sites will be entered on the study centrally by MGH study staff. Study staff from the participating institution will confirm eligibility criteria and fax or email the following documents to study staff at MGH: deidentified signed consent form/s, and a completed eligibility checklist. MGH study staff will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once the patient has been registered, a member from of the MGH Cancer Outcomes Research Program (CORE) team (independent from the study staff) will perform randomization procedures using a computer-generated randomization schema, stratified by study site and transplant type. MGH study staff will fax or e-mail the information about randomization to the study staff at the participating site. MGH study staff may also call the research nurse or data manager at the participating site to verbally confirm registration and randomization.

5.2 Site Investigators and Study Staff Training:

We will conduct an in-person centralized training at MGH for the site lead investigators (site PIs) and RAs to ensure consistent recruitment and enrollment procedures across study sites. We will train the investigative team on: 1) identifying potentially eligible patients via the admission database; 2) tracking potentially eligible patients until their admission for HCT; 3) communicating with oncology clinicians about patient eligibility; 4) obtaining written informed consent from patients and caregivers; and 5) monitoring patients and caregivers longitudinally and administering study questionnaires. Additionally, the site lead investigators will attend the palliative care training described below in-person during their MGH visit.

5.3 Palliative Care Clinician Training

Given heterogeneity in palliative care practices, all participating palliative care clinicians will undergo training and ongoing supervision to ensure that the provision of palliative care services is consistent across study sites. Our research team developed the palliative care intervention guide based on our prior study describing the longitudinal physical and psychological symptom burden in patients undergoing HCT and their caregivers. We refined the intervention guide after conducting qualitative interviews with the palliative care clinicians who participated in our single-site trial. The intervention guide does not manualize the timing of addressing each of the content areas or specific symptoms, as the relevance of the topics (e.g., management of specific symptoms, patient coping, or management of expectations) is dependent on each patient's course during his or her HCT hospitalization. However, it does provide guidance for palliative care clinicians about addressing each content area, when appropriate during the patients' transplant course. We have utilized palliative care intervention guides in our prior multi-site studies to ensure intervention fidelity. Prior to the study start, all participating palliative care clinicians will attend a full-day training using video conferencing to review the intervention guide (the site lead investigators will complete this during their in-person training at MGH). Drs. Jackson and Greer will lead these sessions at MGH. Drs. Jackson and El-Jawahri will also lead monthly supervision calls with the participating palliative care clinicians throughout the trial conduct.

6.0 Multi-Site Research*

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

6.1 Communication across sites

Dr. El-Jawahri and the MGH study team will be responsible for managing communication with all participating sites. Dr. El-Jawahri will conduct a monthly phone call with the site-Principal Investigators to ensure adequate oversight on the following:

- Understand and communicate the policies and processes of IRB, and be familiar with the research.
- Assist participating sites in obtaining local IRB approval for the protocol.
- Ensure that all participation sites will have the most current version of the protocol, consent document, and HIPAA authorization.
- Ensure that all required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- Ensure that all modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
 - All local site investigators conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

6.2 Methods of communication with participating sites:

Dr. El-Jawahri will lead a monthly meeting with participating sites to discuss study progress and any issues or concerns as they arise. Given this is a supportive care study, we do not anticipate any serious adverse events to be related to participating in the study. However, participating sites will contact the MGH team either via telephone or email to report any adverse events within 48 hours of their occurrence.

6.3 Data Storage to maintain confidentiality

All patient information will remain confidential and stored on Partners computers and in REDCap. Since these records necessarily contain patient identifiers, only study staff will have access to them. 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. Data abstracted from the Electronic Health Record will be maintained in REDCap. REDCap is a free, secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data collection projects rely on a study-specific data dictionary defined by members of the research team with planning assistance from Harvard Catalyst and The Harvard Clinical and Translational Science Center EDC Support Staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides flexible features that can be used for a variety of research projects and provides an intuitive interface to enter data with real time validation (automated data type and range checks). The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

7.0 Study Timelines

Table 1 depicts the expected study timeline:

Time Point	Table 1: Study Procedure
Months 0-2	Finalize protocol development and submit to Institutional Review Board approval
Months 3-6	<p>Staff Training</p> <ul style="list-style-type: none"> ❖ Hire RAs at each site and train them in study procedures, recruitment, and data collection. ❖ 2-day visit to Boston for Duke and Fred Hutchinson investigators and RAs to finalize study standard operating procedures. ❖ 1-day palliative care clinician training (in-person for co-investigators) and via video conference to review the palliative care intervention guide and on use of REDCap.
Months 7-43	<p>Randomized Controlled Trial:</p> <ul style="list-style-type: none"> ❖ Enroll and randomly assign 360 patients (180 per study group) to receive either inpatient integrated palliative and transplant care vs. transplant care alone across three study sites. ❖ 2-day visit to Boston for Duke and Fred Hutchinson investigators and research assistants to review study progress and assess the fidelity of data collection and data entry (month 20).
Months 44-56	<p>Data Collection:</p> <ul style="list-style-type: none"> ❖ Complete longitudinal data collection with a minimum of 1 year follow-up on all study participants. ❖ 2-day visit to Boston for Duke and Fred Hutchinson investigators and research assistants to review outcome measures and plan for dissemination of study findings (month 53).
Months 57-60	<p>Data Analysis:</p> <ul style="list-style-type: none"> ❖ Complete data analysis and submit primary manuscripts. ❖ Prepare and submit grant proposal for large scale multi-site dissemination and implementation study.

Each subject will be enrolled for approximately one year to collect patient-reported outcomes. We estimate that we will complete the primary manuscripts in months 57-60 from the study start period.

8.0 Study Endpoints*

8.1 Primary endpoint:

- Compare patient QOL (FACT-BMT) scores at week 2 between the study groups

8.2 Secondary endpoints:

- Compare patients' QOL (FACT-BMT) longitudinally between the study groups
- Compare patients' symptoms (ESAS) scores between the study groups
- Compare patients' fatigue (FACT-fatigue) scores between the study groups
- Compare patients' depression and anxiety symptoms (HADS and PHQ9) between the study groups
- Compare patients' post-traumatic stress symptoms (PCL-C) between the study groups
- Compare caregivers' QOL (CARGOQOL) scores between the study groups
- Compare caregivers' anxiety and depression symptoms (caregiver HADS and PHQ9) between the study groups

8.3 Exploratory endpoints

- Compare patient coping (Brief Cope) between the study groups

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

- Compare caregiver coping (Brief Cope) between the study groups
- Assess whether group differences in patient-reported QOL (FACT-BMT) are mediated by improved symptom burden (mediator: ESAS/HADS), or coping (mediator: Brief Cope)
- Assess whether patient or transplant related characteristics are moderators of the impact of palliative care intervention on patient-reported QOL

9.0 Procedures Involved

9.1 Study design

We propose a multi-site randomized controlled trial of inpatient integrated palliative and transplant care versus transplant care alone in 360 patients with hematologic malignancies hospitalized for HCT and 180-360 of their caregivers. Patients will be randomized in 1:1 fashion and stratified by study site and transplant type (autologous vs. allogeneic). As autologous and allogeneic HCT have significantly different courses of recovery post-transplant,¹ we will stratify by the type of transplant to ensure adequate and balanced representation between the two study groups

9.2 Palliative Care Intervention:

Patients randomized to the palliative care intervention will meet with a palliative care clinician within 48 hours of randomization (excluding weekends). After the initial visit, the palliative care clinicians will meet with patients at least two times per week during their hospitalization. Patients, caregivers, or the palliative care clinician may initiate additional visits as needed.

Table 2: Palliative Care Intervention Domains		
Domain	Elements	Key Points
Therapeutic Relationship	<ul style="list-style-type: none"> • Introducing role palliative care • Understanding the patient and caregiver experience • Building trust with the patient and caregiver 	<ul style="list-style-type: none"> • Develop a strong therapeutic relationship with patients and caregivers • Learn about the values, life goals, and experiences of patients and their caregivers both prior to and after the cancer diagnosis • Develop trust and credibility with patients and caregivers by providing reassurance and outlining parameters of communication
Assessment and Treatment of Patient Symptoms	<ul style="list-style-type: none"> • Preparing for symptoms • Assessing & treating symptoms • Coordinating symptom management with HCT team • Providing referral for symptom management 	<ul style="list-style-type: none"> • Clarify the symptoms the patient will likely experience and offer reassurance about the methods for reporting and treating symptoms • At every visit, elicit existing and new symptom concerns with emphasis on common HCT symptoms (nausea, pain and mucositis, fatigue, sleep disturbances, constipation, diarrhea, anxiety and depression) • Maintain ongoing, effective communication with HCT clinicians to define mutual collaboration and work within their preferred practice patterns • Emphasize team approach to care by referring to specialty care, mental health, alternative medicine, and spiritual support as needed
Managing Patients and Caregivers Expectations	<ul style="list-style-type: none"> • Reviewing in-detail the expected illness trajectory during HCT • Ensuring accurate expectations throughout the HCT process • Enhancing patients' and caregivers' understanding and acceptance of the illness 	<ul style="list-style-type: none"> • Address early on patients and caregivers' concerns about the trajectory of illness during HCT and treatment side effects • Reassure patients and caregivers that QOL deterioration is expected, temporary and does not indicate worsening health status or unsuccessful HCT • Recognize that illness acceptance involves cognitive, emotional, and behavioral elements and offer a safe venue for patients and caregivers to ask questions about their disease and HCT process
Coping with Illness and HCT	<ul style="list-style-type: none"> • Reviewing & validating prior coping efforts • Discussing & advocating for different methods of coping 	<ul style="list-style-type: none"> • Recognize that patients and caregivers bring their own expertise in coping to the current circumstance based on prior experiences • Introduce strategies to help improve adjustment (e.g., behavioral, cognitive, and spiritual approaches; accepting illness while maintaining hope; social support)

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

	<ul style="list-style-type: none"> • Supporting caregiver coping • Providing referral for additional support 	<ul style="list-style-type: none"> • Bolster caregiver coping by assessing burden, enhancing their communication with patients, and recommending additional support • Involve other members of the team for patients and caregivers who may be experiencing severe distress (e.g., social work, psychology)
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As shown in Table 2 above, the palliative care intervention will focus on the following content areas: 1) addressing patients' physical and psychological symptoms; 2) managing patients' and caregivers' expectations; and 3) providing patients and caregivers with strategies to cope with the illness during HCT. Palliative care clinicians will focus specifically on symptoms we have shown to be prevalent in this population, including nausea, pain and mucositis, fatigue, sleep disturbances, constipation, diarrhea, anxiety and depression.

Ensuring Fidelity of the Palliative Care Intervention: We will take several steps to ensure the fidelity of our study design, training, and intervention delivery as noted in the table below (Table 3). Specifically, for the study design, we will utilize an evidence-based palliative care intervention guide, measure the number and duration of palliative care visits, and monitor the number of participants in the control arm receiving palliative care. Also, we will employ rigorous training procedures with in-person training for site PIs and RAs; and monthly telephone conferences with Drs. El-Jawahri and Jackson with the site PIs and palliative care clinicians to discuss any issues. To ensure the fidelity of the intervention delivery, we will review palliative care clinicians' documentation to enable us to assess the content of the clinical encounter. Drs. Greer and El-Jawahri will independently review electronic surveys completed by the palliative care clinicians to ensure intervention fidelity and conformity between sites in addressing the domains and topics as specified by the guide. Based on this review, Drs. Greer, El-Jawahri, and Jackson will provide constructive feedback as needed to individual clinicians to ensure they are delivering the intervention in a consistent fashion. The site PIs will also review palliative care notes in the health record to ensure adherence to the intervention guide content and provide feedback to clinicians at the site research meetings.

Table 3: Fidelity	Steps Taken to Ensure Fidelity	Fidelity Assessment
Study Design	<ul style="list-style-type: none"> - Intervention based on a well-defined conceptual model and systematic review of literature - Standard intervention dose with clear feasibility data based on prior work - Cross-contamination not expected to be a major issue given lack of palliative care consults in HCT 	<ul style="list-style-type: none"> - Utilize evidence-based palliative care intervention guide based on prior trial - Measure number of intervention visits & visit duration using the palliative care clinician survey - Measure number of participants in standard-of-care receiving palliative care
Training	<ul style="list-style-type: none"> - Use if a palliative care intervention guide - Initial in-person training of site PIs on study protocol and palliative care intervention - Initial in-person training of site RAs on study procedures - Initial full-day training of all palliative care clinicians (all sites) with Drs. Jackson and Greer using video conferencing - Monthly conference calls (led by Drs. El-Jawahri & Jackson) with site PIs and palliative care clinicians to address study issues - Annual retraining seminar via video conferencing with all palliative care clinicians (at all sites) 	<ul style="list-style-type: none"> - Complete review of intervention guide - Complete training of all site-PIs in protocol administration and intervention delivery - Complete training of all site RAs on protocol and study procedures - Assess pre- and post-knowledge that palliative care clinicians acquired during training - Send meeting minutes from conference calls to all site PIs, palliative care clinicians, and research assistants - Assess pre- and post-knowledge that palliative care clinicians acquired during retraining
Intervention Delivery	<ul style="list-style-type: none"> - Utilization of palliative care intervention guide with standardized content areas - Completion of electronic survey after each encounter to record the content and topics that palliative care clinicians addressed during the visit and audio-record of all palliative care visits - Documentation of clinical encounter using standardized visit note template in site medical record 	<ul style="list-style-type: none"> - Conduct ongoing training of any new staff in standardized palliative care intervention guide - Drs. Greer & El-Jawahri will review palliative care electronic surveys monthly for 6 months and then every 4 months thereafter to ensure adherence to content, and Dr. Jackson will review findings during monthly calls. - The site PI will review the first 3 notes for the first 15 participants on the PC arm, and then review 2 palliative care notes for each PC clinician every 6 months thereafter

9.3 Transplant Care Alone:

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

As done in our prior trial,³⁴ patients randomized to the transplant care alone 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 clinicians. In most transplant centers, supportive care measures are instituted at the discretion of the transplant oncology team and include symptom-directed therapies for nausea, pain, and diarrhea. Additionally, social workers are occasionally available to assist in helping patients and families emotionally during the HCT process. We will collect data on social work consultations and consider them as a covariate in our analyses. Patients randomized to transplant care alone will receive all supportive care measures as instituted by the transplant oncology team including social work consultations upon request. We anticipate minimal cross contamination, as the rate of palliative care consultation is less than 5% for patients admitted for HCT at our participating sites. In our prior single center trial, only two patients randomized to transplant care alone received palliative care consultations. Notably, the palliative care intervention did not lead to significant changes in supportive care practices implemented by the transplant clinicians. While patients undergoing HCT often interact post-transplant, they are typically isolated during the acute hospitalization period and have minimal interactions. Patients are also typically seen by multiple providers including nutritionists, physical therapists, residents, nurse practitioners, and social workers. Consequently, patients randomized to transplant care alone will not notice the lack of interaction with palliative care clinicians. Therefore, we do not anticipate that cross-contamination will be a significant issue in the proposed trial.

9.4 Selection of Instruments

We selected instruments based on our prior studies and the conceptual framework of our intervention, which seeks to improve patients' and caregivers' QOL and mood, reduce their symptom burden, and enhance their coping strategies, which will ultimately lead to improvement in their QOL and psychological outcomes post-HCT.

- **Demographics:** Patients and caregivers will complete a demographic questionnaire at baseline detailing their age, sex, race, ethnicity, religion, relationship status (caregivers will specify their relationship with patients), educational level, annual household income, and living situation [appendix A].
- **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 HCT.⁵³ 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]⁵⁴.
- **QOL-Caregiver:** We will use the CareGiver Oncology QOL questionnaire (CarGOQOL) to measure caregiver QOL. The CarGOQOL is a 29-items well-validated instrument to measure QOL in multiple domains.⁵⁵ The CarGOQOL has been previously

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

validated for caregivers of patients with cancer including hematologic malignancies [Appendix D]

- **Mood (patient & caregivers):** We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety in all study participants (patients and caregivers). The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week [appendix E]⁵⁶. 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 F]⁵⁷.
- **PTSD symptoms - Patient:** We will use the Post-Traumatic Stress Disorder Checklist (PCL) to assess symptoms of post-traumatic stress in patients. 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 G].³⁹
- **Fatigue – Patient:** we will use the 13-item FACT-Fatigue scale to assess fatigue symptoms [appendix H].⁵⁸
- **Coping strategies (patient and caregiver):** We will use the Brief Cope, a 28-item questionnaire that assess 14 methods of coping (e.g., self-distraction, humor, denial) using a 4-point Likert scale [appendix I].⁵⁹

9.5 *Data from the Electronic Health Record:*

Study staff will collect clinical, disease, and transplant characteristics at baseline including: ECOG Performance Status at the time of HCT, clinical comorbidities as measured by the HCT-Comorbidity Index,⁶⁰ underlying diagnosis, date of diagnosis, disease status at the time of HCT, disease risk based on the Disease Risk Index,⁶¹ conditioning regimen, donor type, donor source, date of HCT, and hospital length-of-stay. We will also collect data on the incidence and severity of acute and chronic graft-versus-host disease and the incidence of relapse at one year post-HCT as these outcomes are associated with QOL.

9.6 *Data on Palliative Care Visits:*

As noted previously, palliative care clinicians will enter data on the nature of their initial visit and weekly visits with study participants, using a Research Electronic Data Capture (REDCap) survey. The REDCap survey assesses domains and topics covered during the palliative care visit. We developed and refined the domains of inpatient palliative care and detailed the possible topics addressed under each domain based on our previous trial. In our single center trial, all palliative care clinicians completed REDCap entries after their clinical interactions with patients for 100% of their encounters. We will use the identical study procedures to ensure documentation of all the palliative care clinical interactions in this proposed trial. Specifically, prior to the study start all participating palliative care clinicians will be trained on the use of the REDCap survey and the importance of entering these data. After the initial visit and on weekly

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

basis, the research assistant will send a secure email with the patient's name with a link to the REDCap system. If clinicians do not complete the REDCap entry within 48 hours, they will receive a second email with the site PI included on the email.

Study staff will administer self-report study assessments at baseline, week-2 during the transplant hospitalization (+ 2 day window), at three, six, and twelve months post-HCT (+/- 2 week window). If the patient prefers verbal administration of the assessment, the study staff member will be someone blinded to the intervention assignment. The demographic questionnaire, included in the patient and caregiver baseline assessments only, will ask study participants to provide their email address to allow us to email study assessments to those who do not have a scheduled appointment within the follow-up time points. If patients do not have an email address, we will either send them paper copies of the survey or ask them to complete them verbally over the telephone. We will track the methods of survey completion among participants. The entire study assessment battery will be administered at all time points (except demographics) and takes approximately 20 minutes to complete. The selected self-report measures have strong psychometric properties and have been well validated in previous studies in this population. All study measures are available in both English and Spanish.

9.7 Data collection

We will collect and enter all patient and 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 caregivers who are not present in the hospital during the period of data collection will be provided with remote access to the REDCap system [Appendix L], paper-based questionnaires for home administration [Appendix K], or administration of questionnaire over the phone [Appendix M]. 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 incompleteness. Table 4 details the schedule for administering the self-report measures. All participants (patients and caregivers) will complete baseline evaluation within 72 hours of study enrollment (excluding public holidays, in which case the RA will approach in 96 hours). All participants will then have a second evaluation during their second week of hospitalization for HCT. Patients undergoing autologous HSCT (and their caregivers) will have their second evaluation during the hospitalization on day +5 (48 hour window: day +5 to day +7). Patients undergoing allogeneic HCT (and their caregivers) will have their second evaluation during the hospitalization on day +8 (48 hour window: day +8 to day +10). 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 (and caregivers) will also complete additional questionnaires at 3, 6, and 12 months post-transplantation (+/- 2 week window).

Table 4: Administration of Self-Report Measures

Participant	Baseline	Week-2:(Day+5 auto, day +8 allo)	3, 6, & 12 months (+/- 2 week window)
Patient Measures:			
Demographics	X		
FACT-BMT/Fatigue	X	X	X
ESAS	X	X	X
HADS	X	X	X
PHQ-9	X	X	X
PCL (PTSD)	X	X	X
Brief Cope	X	X	X
Caregiver Measures:			
Demographics	X		
CarGOQOL (QOL)	X	X	X
HADS	X	X	X
PHQ-9	X	X	X
Brief Cope	X	X	X

10.0 Data and Specimen Banking: Not applicable

10.1 Data analysis

Specific Aim 1: To demonstrate the efficacy of inpatient integrated palliative and transplant care for improving patient-reported outcomes: Analyses will begin with descriptive and graphical summaries of the endpoints and evaluation of whether a normality assumption is reasonable for the endpoint or whether transformation is necessary. All statistical tests will be two-sided with an alpha level of 0.05. For all secondary and exploratory outcomes, we will use the false discovery rate (FDR) control method to address the issue of multiple testing. We selected an FDR of 0.15, which denotes the acceptable percentage of results that potentially represent false positives.⁶² The primary endpoint of the study will be to compare patient QOL (FACT-BMT) scores at week-2 between the study groups controlling for baseline values and demographic and clinical factors (as necessary for any imbalances in baseline variables) using a linear regression model. We will also compare secondary endpoints including patients' symptoms (ESAS), fatigue (FACT-Fatigue), depression and anxiety symptoms (HADS and PHQ9), and coping (Brief Cope) at week-2 between the study groups using linear regression models controlling for baseline values and clinical factors (as necessary for any imbalances in baseline variables). In the event that the effect of the intervention differs by transplant type, conditioning intensity, or other patient characteristics, we will examine these variables as interaction terms in the linear regression analyses. Finally, we will compute the effect size and Reliability Change Index to assess practical and clinical significance in the degree of change in the primary and secondary outcomes.

We will also utilize linear mixed models of the longitudinal data, allowing us to account for dependency among means over time and to control for demographic and clinical factors (as necessary for any imbalances in baseline variables) when examining change between groups in outcomes of interest across multiple time points (i.e., baseline, 2 weeks, 3, 6, and 12 months post-HCT). We will estimate practical and clinical significance of these outcomes (Cohen's d and Reliability Change Index).

Specific Aim 2: To assess the impact of inpatient integrated palliative and transplant care on caregiver-reported QOL and psychological outcomes: We will similarly compare caregivers' QOL

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

(CARGOQOL), depression and anxiety symptoms (caregivers HADS and PHQ9), and coping at week-2 using linear regression models controlling for baseline values and clinical factors (as necessary for any imbalances in baseline variables). We will also use linear mixed models of the longitudinal data, allowing us to account for dependency among means over time and to control for demographic and clinical factors (as necessary for any imbalances in baseline variables) when examining change between groups in outcomes of interest across multiple time points (i.e., baseline, 2 weeks, 3, 6, and 12 months post-HCT). We will again estimate practical and clinical significance of these outcomes (using Cohen's d and Reliability Change Index).

Specific Aim 3: To explore mediators and moderators of the effect of the palliative care intervention on patient-reported QOL: We will conduct bootstrapped tests of mediation to determine whether group differences in patient-reported QOL (FACT-BMT) are mediated by improved symptom burden (mediators: ESAS/HADS), or coping (mediator: Brief Cope). Although in our randomized trial, we did not identify moderators of the effect of the palliative care intervention, we will test for potential moderators to ensure generalizability of our findings, as other studies have found age and gender as moderators of the impact of palliative care in patients with lung cancer.⁶³ We will create interaction terms for the linear regression analyses and linear mixed models to examine whether differences in patient-reported QOL are moderated by patient factors (age, gender, race), transplant factors (type of HCT, conditioning intensity), or study site.

Missing Data: The analyses will initially focus on the study completers to estimate the effect of the integrated palliative care intervention in patients undergoing HCT (and their caregivers) who completed the protocol as intended without imposing assumptions about missing data. We will also use the intention-to-treat principle with all randomized subjects, conducting sensitivity analyses to explore how various assumptions about missing data and differences between completers and non-completers affect the estimated outcomes. If data appear to be missing at random, we will employ multiple imputation methods⁶⁴, maximum likelihood estimate approach with EM algorithm⁶⁵, and mixed-effects modeling⁶⁶ that can adequately account for data missing at random. However, if we find that participants do not complete the study because of disease worsening, suggesting missing data are not random, we will employ pattern mixture modeling or joint modeling approaches⁶⁷ to handle incomplete data, and perform sensitivity analysis⁶⁸ to assess the impact of missing data.

10.2 Sample Size Calculation & Power Analysis:

Although we observed a large effect size for our palliative care intervention on patient-reported QOL during hospitalization (primary endpoint, Cohen's d = 2.9), we chose to be conservative in estimating the sample size for this trial given the proposed testing of the effect of the intervention on caregivers and post-HCT outcomes, expected attrition over time, and the proposed tests of mediation and moderation. In our prior study, we observed a 6.9 point difference (SD = 20) in QOL at week-2 between intervention and control group. With a sample size of 360, we will have 87% power to detect at least 6.9 point difference in patient QOL at week-2 between groups with a two-sided 0.05 significance level and assuming 10% missing data at week-2. Importantly, we only had 2% and 6.9% missing data at week-2 and 3-months post-HCT in our prior study. With a sample size of 360, we will also have > 80% power to detect a treatment difference in secondary patient-reported outcomes at week-2 (symptom burden, depression, and anxiety) with a two-sided 0.05 significance level. Assuming a missing data rate of 15% at three and six months, we will have 80% power to detect a 4.3 point difference in patient-reported QOL at 3 and 6 months post-HCT between the two groups (based on the difference we detected in our previous study). In our prior trial, we enrolled 94 (56%) caregivers and we noted a 1.6-point difference (SD = 3.3) in caregiver HADS-depression scores between the two study groups at week-2. Assuming that we enroll caregivers

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

for 50% of the patients included in this study (n = 180), we will have 90% power to detect a 1.6-point difference in caregiver HADS-depression scores at week-2 between the two groups with a two-sided 0.05 significance level.

10.3 Data security

Patient data will be collected at each institution (MGH, Duke, and Fred Hutchinson Cancer Research Center) using REDCap. Each site will maintain their own separate list of patient names and study IDs, which will be saved in password-protected files. Participants will be identified on study forms by case number only to protect confidentiality. 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 has been completed as discussed previously. At the completion of the study, de-identified data files will be transferred from Duke and Fred Hutchinson to the MGH using a secure data transfer.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the research team. Under these circumstances, as clearly stated in the patient consent form, the study RA will inform the site PI. The site PI will then determine the need to involve social work, psychiatry and/or take further action as deemed necessary.

In addition, as stated previously, all study staff at all participating sites will undergo an extensive training on study procedure and study procedures as well as data management to ensure data security and maintaining of confidentiality.

10.4 Quality control for collected data:

Our study staff will utilize double-data entry for approximately 10% of the data entered through REDCap to ensure high data quality. A research coordinator, blinded to the study intervention, will double enter 10% of the data through REDCap to check on data fidelity. If an error is found, the research coordinator will double enter an additional 5% of the data through REDCap. This process will continue until no errors are found.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Purpose of Multi-Center Data and Safety Monitoring Plan:

The purpose of the multi-center data and safety monitoring plan is to establish standards that will ensure that this Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable Dana Farber Harvard Cancer Center (DF/HCC) Standard Operating Procedures. Please see Appendix O for full details regarding Data and Safety Monitoring Plan.

General Roles and Responsibilities:

The overall PI (Dr. El-Jawahri) will work closely with Dr. Temel (co-investigator), who has expertise in conducting multi-site randomized palliative care trials, to ensure the successful implementation of the proposed multi-site project. Dr. El-Jawahri will be responsible for all aspects of conducting the multi-site protocol, which includes:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and participating institutions are qualified and appropriately resourced to conduct the protocol.
- Include a Multi-Center Data and Safety Monitoring Plan as detailed in this document and appendix O.
- Ensure all participating institutions are using the correct version of the protocol.

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

- Ensure that each participating investigator and study team member receives adequate protocol training and a site initiation visit prior to enrolling participants and throughout the trial's conduct as needed.
- Monitor progress and overall conduct of the study at all participating institutions.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, Dana Farber Harvard Cancer Center requirements, HIPAA requirements, and the approved protocol.
- Commit to provisions that the protocol will not be rewritten or modified by anyone other than the overall PI.
- Monitor accrual and address participating institutions that are not meeting their accrual requirements.

The Massachusetts General Hospital Cancer Center as the overall Coordinating Center will have the following responsibilities:

- Review registration materials for eligibility and register participants from participating institutions.
- Distribute protocol and informed consent document updates to participating institutions as needed.
- Oversee the data collection process from participating institutions.
- Maintain documentation of Serious Adverse Events (SAE) reports and deviations/violations submitted by participating institutions.
- Distribute SAEs that fall under the IRB Adverse Event Reporting Policy to all participating institutions.
- Maintain regulatory documents of all participating institutions which include but not limited to the following: local IRB approvals/notifications from all participating institutions, confirmation of Federal wise Assurances (FWAs) for all sites, all SAE submissions, screening logs for all sites, IRB approved consents for all sites.
- Conduct regular communications with all participating institution and maintain documentation of all relevant communications.

Each participating institution is expected to comply with all applicable federal regulations and requirements, the protocol and HIPAA requirements. Each participating institution will be responsible for the following:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files.
- Provide the MGH Cancer Center with regulatory documents or source documents as requested.
- Participate in protocol training at the MGH Cancer Center during the initial study visit prior to enrolling participants.
- Participate in the two additional site visits to MGH throughout the study period.
- Update the MGH Cancer Center with research staff changes on a timely basis.
- Submit SAE reports to local IRB per local requirements and to the MGH Cancer Center, in accordance with the DF/HCC requirements.
- Submit protocol deviations and violations to the local IRB per local requirements and to the MGH Cancer Center in accordance with DF/HCC requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

Intervention Training and Supervision:

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

- Intervention Training: We will use the inpatient palliative care intervention guide developed by Drs. El-Jawahri, Jackson, and Greer in our previous single center randomized trial. As described in the study procedures section, Drs. Jackson and Greer will provide initial training for all palliative care clinicians from all participating institutions using video conferencing to review the intervention guide (The site lead investigators will attend this training in-person). Dr. Jackson will serve as the primary supervisor for the palliative care clinicians delivering the intervention.
- Assessment of Intervention Fidelity: To ensure the appropriate delivery of the palliative care intervention, Drs. Jackson, Greer, and El-Jawahri will participate in monthly telephone conferences with the investigators and palliative care clinicians at participating sites to discuss any issues or concerns regarding the intervention. Moreover, palliative care clinicians will complete electronic surveys using Research Electronic Data Capture (REDCap) to report on the domains covered during their palliative care visits. Our research team has extensive experience using REDCap and utilized it in our prior study to collect information from palliative care clinicians about each clinical encounter. The brief REDCap Survey assesses domains and topics covered during the palliative care visit. We developed and refined the domains of inpatient palliative care and detailed the possible topics addressed under each domain based on our previous randomized trial. Drs. El-Jawahri and Greer will review the palliative care electronic surveys monthly for the first six months and then every 4 months thereafter to ensure adherence to the content of the intervention as specified by the intervention guide.

Informed Consent Requirements:

The Dana Farber Harvard Cancer Center approved informed consent document will serve as a template for the informed consent for participating institutions. The participating institution consent form must follow the consent template as closely as possible. Participating institutions are then to send their version of the informed consent document and HIPAA authorization, if a separate document, to the MGH Cancer Center for review and approval prior to submission to their local IRB. For all future consent versions, the approved consent form must also be submitted to the MGH Cancer Center after approval by the local IRB.

Multi-Center Protocol Confidentiality: All documents, investigative reports, or information relating to the participants are strictly confidential. Confidentiality is assured as participants will be identified on all study materials only by participant number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified,' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996. Each participating site will keep participant data in computer file that is password protected and will change this password whenever the staff changes. Only the Principal Investigators and study staff will have access to the data. We will keep a link between participant number and participant's name in a separate file, also password-protected (with a different password).

Data Management Organizational Structure: Data forms will undergo a systematic and rigorous editing process prior to being keyed into the database. The research assistants at each participating site will routinely evaluate the data and discuss any problems and questions with the study staff, site-PIs, and the investigator team at the regular weekly team meetings. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated once a month during the final team meeting of the month at each participating site. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available.

Attrition Safeguards/Protection of Loss of Data:

A notable methodological consideration pertaining to the proposed research is protection against attrition. Our research group has conducted numerous clinical intervention studies. In our previous work, we have learned that individuals are best retained in studies when there is 1) a familiarity with study personnel (e.g., ability to

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

effectively establish rapport), 2) team-based persistence in conducting follow-up assessments, and 3) intervention sessions happening in tandem with ongoing medical appointments or inpatient hospitalizations. Yet, it is worth noting here a number of key issues that we have thoughtfully considered in the construction of the present proposal related to attrition. Attrition in clinical research studies overall occurs from three major sources: (a) disease worsening/mortality, (b) refusal to participate, and (c) loss of contact.

- **Disease Worsening/Mortality:** Given the burden of therapy for patients with hematologic malignancies undergoing HCT, we do anticipate that a minority of participants will be unable to complete the study protocol due to deteriorating health or death. Our research team has given considerable thought to this concern and adequately powered the study to account for missing data. In our prior single center randomized trial of the inpatient palliative care intervention, we only had 2% and 6.9% missing data at week-2 and 3-months post-HCT. We anticipate this percentage to be slightly higher in the proposed multi-site randomized trial given the multi-site study design and the inclusion of additional longitudinal assessments at six months and one year post-HCT. Nonetheless, the study research assistants will maintain detailed records for patient attrition due to disease-related factors at each participating site.
- **Refusal to Participate:** Participants who are successfully recruited into the study but later refuse to participate in subsequent intervention sessions pose a threat to the proposed study. In our previous trial, our refusal to participate rate after study enrollment was quite low at less than 1%. Again, the study research assistants will maintain detailed records for patient refusals at each participating site.
- **Loss of Contact:** Another source of attrition involves those subjects who are successfully recruited into the study but who cannot be located for subsequent follow-up assessments. Like attrition due to subject refusal, attrition due to loss of contact poses a threat to the proposed study. We do not anticipate this to be a major issue for the proposed study given the intensive and frequent outpatient follow-up visits for patients with hematologic malignancies during the first six months to one year post-HCT.
- **Participant Adherence:** To minimize attrition, we plan to use multiple strategies to reduce drop-out. Potential participants will be invited to participate in the baseline assessment during which time participants will receive a thorough explanation of the study treatments, requirements, and follow-up procedures. Study staff will emphasize the patient's responsibility as a research participant, reiterate confidentiality, and work to develop good rapport. Since the palliative care intervention occurs during the inpatient hospitalization for HCT, we do not anticipate any problems with adherence to the intervention visits. We will make a concerted and systematic effort to facilitate adherence to the completion of follow-up assessments. This task will be accomplished by: (1) obtaining longitudinal participant-reported measures during regular follow-up appointments; (2) providing participants with remote access to complete the longitudinal study measures; and (3) making reminder phone calls and administering the study measures over the phone if necessary for participants who do not have appointments in the window for assessment completion.

Data Safety and Monitoring Plan

The following procedures will be followed, in compliance with NIH requirements, to ensure the safety of study participants and the validity and integrity of data.

- **Range of Safety Reporting:** The research team (Drs. El-Jawahri, Temel, and Greer) will review all data pertaining to safety during their weekly meeting. The site PIs will also review all data pertaining to safety at their weekly site research meetings. These include adverse events (AEs) and SAEs, but also other data that may reflect differences in safety such as treatment retention rates and reasons for dropout. Dr. El-Jawahri will also lead a monthly meeting with all sites to discuss any issues pertaining to participant safety and data fidelity.
- **Data Repository:** The research team at the MGH Cancer Center has coordinated research initiatives over the past eight years that have established procedures and technologies for data collection and management. Dr. El-Jawahri will oversee all aspects of data collection for the study and the research assistants will have the operational responsibility of data management. Specifically, the research team will develop a study specific

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

data management protocol and standard operating procedures for the creation and testing of all study forms, data collection, quality control, and data extraction. These forms will be standardized. We will provide ongoing oversight of data management throughout the study, and will be responsible for generating reports and datasets for quality control and data analysis. All data management activities will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. REDCap provides secure, HIPAA compliant, web-based applications with an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry.

- **Serious Adverse Events:** Expedited review will occur for all events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. Given that this is a supportive care study in a population at risk for disease relapse and death due to transplant complications (unrelated to the study procedures), only SAEs that may potentially be related to the study will be reported to the IRB. All relevant information will be reported to the IRB for each SAE including information about the event and its outcome, study condition, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by secure e-mail of all related study forms shall be made to the IRB within 24 hours of the occurrence of any SAE that might be relevant to the study. Information will be reviewed and a determination made of whether there was any possible relevance to the study interventions. Additional reporting to the NIH will be made according to their respective regulations governing SAE reporting. We do not anticipate that any SAEs will result from participation in the study.
- **Non-Serious Adverse Events:** The research team will review monthly summary reports of the numbers and rates of adverse events by treatment group and study site. These reports will include types of events, severity, and treatment phase.
- **Other Safety-Related Reports:** The research team will review weekly summary reports of treatment retention and reasons for dropout, by treatment group and study site.

Monitoring of Data Quality by the research team:

The research team (at each participating institution) will review the following items on weekly basis to ensure data quality and completeness:

- Total enrollment compared with anticipated enrollment
- Number of ineligible patients registered
- Proportion of missing participant-reported outcomes
- Proportion of other missing data
- Number of participants lost to follow-up
- Number of participants completing the study

Additionally, the research team (at each participating institution) will receive a report on safety and outcome data for the trial:

- Number of deaths, listed by cause
- Number and types of SAEs
- Number and types of reportable AEs
- Number of participants with primary outcomes
- Number of participants with secondary outcomes

12.0 Withdrawal of Subjects*

We do not anticipate that any research participants will be withdrawn from the study without their consent. If a participant requests withdrawal from the study, we will ask them if they are comfortable sharing the reason for withdrawal to ensure that there are no adverse events to report to the IRB. We will ask the study participant if they are still willing to permit the study team to continue to monitor their health record, but withdraw from all other study procedures.

13.0 Risks to Subjects*

Given that this study is a palliative care intervention, we do not anticipate any study-related events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This study population is comprised of individuals undergoing HCT who frequently experience disease worsening, high rate of symptoms, and hospitalizations from the underlying disease and/or side effects of treatment. Therefore, regular fluctuations in cancer-related symptoms, disease worsening, hospitalizations, emergency department visits, and deaths are to be expected throughout the study, and we will not consider or report such events as SAEs in this trial.

Non-Serious Adverse Events: The IRB will be provided with unblinded summaries of study related non-serious adverse events by treatment group at the continuing reviews. These reports will include types of events, severity, and treatment phase. To date, we have had very few non-serious events in our supportive care studies.

As this is a behavioral study, there are no ingested medications, and no biomedical procedures. It is unlikely that participants will be at any risk for physical harm as a result of study participation.

Participants may find some of the questions asked in the questionnaire to be emotionally upsetting, and may experience some fatigue from the length of the assessment battery. As this is a study targeting symptoms that are debilitating and interfere with QOL, it is possible that some participants will experience depression.

Reaction management: A detailed consent form will be signed by each participant or participants will provide verbal consent following the explanations by the RA. The consent form will include all study procedures, information about potential risks and benefits of participation, and information regarding whom the participant can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their medical care. All study staff will complete the required human subjects training before working on any human subject aspects of the study.

Should a participant exhibit or express distress, they will be reassured by the study staff that they need not answer any questions they find upsetting. They will also be reminded that study participation is voluntary. If participants remain distressed, both the site-PI and the primary transplant clinician 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 a participant reports severe distress or suicidal ideation during the study conduct, the RA will inform the site-PI. The site-PI will determine the need to involve psychiatry and take further action as deemed necessary. The research team will review sensitive items regarding suicidal ideation within 120 hours (5 business days) of receipt of completed surveys and will report any suicidal ideation to the site-PI promptly.

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

14.0 Potential Benefits to Subjects*

Early palliative care is recommended as the standard of care for patients with advanced solid tumors. Outside of a clinical trial, patients with hematologic malignancies and those undergoing HCT rarely receive palliative care services. Therefore, a potential benefit of the proposed research to human subjects is that participants may experience benefits from receiving the palliative care intervention. Additionally, some participants may enjoy the opportunity to complete study measures and reflect on their illness experience. Some may also value the possibility that their contribution to the study may benefit other patients with hematologic malignancies. It is also possible that some participants may not derive these benefits. However, the risk from participation in the study is small (and will be minimized by the procedures outlined above), and overall risk to benefit ratio is favorable.

15.0 Vulnerable Populations: Not applicable

16.0 Community-Based Participatory Research: Not applicable

17.0 Sharing of Results with Subjects:

Given the nature of the population included in the study, it is not appropriate to proactively contact participants at the conclusion of this study. We anticipate that a significant proportion of our participants will die during or within months of completing the study. We do not wish to cause unnecessary distress to participants' family members by attempting to contact participants who have died. Therefore, we provide the research team contact information to each participant and encourage them to contact us if they would like to receive updates and information on the research findings.

18.0 Setting

18.1 Location

As stated previously in the recruitment and enrollment procedures (section 5.1), patients will be approached for study participation on the Blood and Marrow Transplant Inpatient Unit at participating sites. For completion of follow-up assessments, participants can be approached on the inpatient unit or during their ambulatory oncology clinic appointments.

19.0 Resources Available

19.1 Team Qualification and oversight

The overall PI of the project (Dr. El-Jawahri) is responsible for full oversight of the project at MGH and participating institutions. She will be meeting with the research coordinator on weekly basis (and more often as urgent issues arise) to ensure the study process is being followed accurately and to address potential challenges or issues as they may arise. The site PI at participating institutions will also hold weekly meetings with their research coordinators to discuss any study issues. The MGH based team will also hold a monthly meeting with participating sites to review the consort diagram, recruitment and enrollment procedures, and any potential problems or issues related to the study operations. Dr. El-Jawahri is a member of the MGH Cancer Outcomes Research Program (CORe). CORe has extensive experience conducting multi-site randomized clinical trials of supportive care interventions in oncology and has the necessary expertise to ensure the success of the proposed project.

19.2 Other Resources

The participating transplant centers perform approximately 250-270 inpatient transplants per year. We anticipate that 10% of patients would be ineligible for study participation. Therefore, we will have

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

approximately 225 patients eligible for study participation per year. We successfully enrolled 86% of potentially eligible patients in our prior single center trial of integrated palliative and transplant care. With centralized research staff training, we conservatively estimate enrolling at least 60% of eligible patients to meet our recruitment goal of approximately 130-135 subjects per year during the three-year enrollment period. In our prior single-center trial, we successfully enrolled 56% of caregivers. Therefore, we anticipate enrolling at least 50% for caregivers in the proposed project.

Dr. El-Jawahri currently has 75% of her time protected to conduct research activities. She will dedicate at least 20% of her time specifically for this project. The site-PIs will dedicate at a minimum 10% of their effort towards ensuring the success of the proposed project.

If participants exhibit distress due to study procedures, both the PI and the primary oncology clinician will be notified. The transplant social workers at all participating sites have also agreed to help with any distress experienced by study participants (patients and caregivers).

To ensure adequate training for all research staff, we will conduct an in-person centralized training at MGH for the lead site investigators (site PIs) and research coordinators to ensure consistent recruitment and enrollment procedures across study sites. We will train the investigative team on: 1) identifying potentially eligible participants via the transplant admission database; 2) tracking potentially eligible patients until their admission for transplant; 3) communicating with the oncology clinicians about participants' eligibility; 4) obtaining written informed consent from patients and caregivers; and 5) monitoring patients and caregivers longitudinally and administering study questionnaires.

20.0 Prior Approvals

We will obtain IRB approval at each of the participating sites prior to initiating any study procedures.

21.0 Recruitment Methods

As stated previously in section 5.1, we will use the same successful recruitment and enrollment procedures from our prior single center trial. Prior to the study start, the site investigators will meet with the transplant oncology team to review recruitment and enrollment procedures. Specifically, the RA will send an email to the transplant clinicians to notify them that their patient (and caregiver) is eligible for study participation and inquire about any concerns regarding their participation. If the clinicians have objections to their patients' and/or caregivers' participating in the study, the RA will document the reason and not approach those individuals. If the transplant clinicians have no objections, the RA will approach patients for study participation two weeks prior to their admission date or within 72 hours of their admission for HCT (excluding public holidays, in which case the RA will approach within 96 hours). The RA will conduct informed consent procedures with potential participants and obtain written informed consent or verbal consent. Patients will then be asked to identify a caregiver who might be interested in participating. Patients without a willing or interested caregiver will still be eligible to participate in the study. The caregiver will be eligible to enroll in the study either at the same time as the patient or within 72 hours after the patient provides written informed consent or verbal consent. We will have a separate consent form for caregivers, which will similarly detail the study procedures. Caregivers will have the option of enrolling in the study in-person with a written informed consent or over the telephone with a verbal consent (Appendix N). Patients and/or caregivers who refuse study participation

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

will be asked the reason for deferring. Study participants will complete baseline self-report assessments on the same day as providing written informed consent or verbal consent.

Patients and caregivers who speak Spanish will have all study procedures and information regarding risks, benefits and study contacts explained to them orally via the use of an interpreter as a first preference, or family member as a second preference. Spanish speaking participants will be given the DF/HCC Spanish consent short form for signing, as well as a copy of the full English consent form for their own reference. Both the Spanish consent short form, and the full English consent form will be signed by the participant, and by a witness. The witness will be either an interpreter or a family member.

Patients will complete baseline self-report assessments at the time of obtaining informed consent for the study, within the two-week window prior to their admission date, or within the 72-hour (excluding public holidays) window from admission to the transplant unit. Patients who provide informed consent and complete baseline questionnaires are then registered with the Clinical Trials Management System. If patients provide consent, but do not complete baseline questionnaire, they will not count towards accrual numbers. Caregivers will have 72-hours from patient enrollment to enroll in the study and complete baseline self-reported measures. If caregivers sign the consent, but do not complete baseline questionnaire, they will not count towards the caregiver accrual numbers. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur prior to the initiation of protocol-specific procedures or assessments.

For registration of patients from DF/HCC institutions, study staff will complete the DF/HCC protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol and the criteria on the eligibility checklist.

Patients from other investigative sites will be entered on the study centrally by MGH study staff. Study staff from the participating institution will confirm eligibility criteria and fax or email the following documents to study staff at MGH: deidentified signed consent form/s, copy of baseline assessment, and a completed eligibility checklist. MGH study staff will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once the patient has been registered, a member from the CORE Program research team (independent from the study staff) will perform randomization procedures using a computer-generated randomization schema, stratified by study site. MGH study staff will fax or e-mail the information about randomization to the study staff at the participating site. MGH study staff may also call the research nurse or data manager at the participating site to verbally confirm registration and randomization. Participants will not receive any payments or incentives for study participation.

22.0 Local Number of Subjects

We anticipate that we will recruit approximately 120-140 patients and up to 120-140 caregivers locally during the study period.

23.0 Provisions to Protect the Privacy Interests of Subjects

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

Patient data will be collected at each institution (MGH, Duke, and Fred Hutchinson Cancer Research Center) using REDCap. Each site will maintain their own separate list of patient names and study IDs, which will be saved in password-protected files. Participants will be identified on study forms by case number only to protect confidentiality. 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 has been completed as discussed previously. At the completion of the study, de-identified data files will be transferred from Duke and Fred Hutchinson to the MGH using a secure data transfer.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the research team. Under these circumstances, as clearly stated in the patient consent form, the study RA will inform the site PI. The site PI will then determine the need to involve social work, psychiatry and/or take further action as deemed necessary.

24.0 Compensation for Research-Related Injury

We do not anticipate any research-related injury due to involvement in this supportive care trial.

25.0 Economic Burden to Subjects

We do not anticipate any financial burden on study participants. Palliative care consultation are covered under the cost of participants' transplant hospitalizations and patients will not be billed personally for these costs. Insurance approval for transplant hospitalization is a requirement at all participating sites.

26.0 Consent Process

As stated previously, the RA will obtain written informed consent or verbal consent for patients participating in the study in a private hospital room. Patients have two weeks prior to their admission date or up to 72 hours from transplant hospital admission to consent for the study (excluding public holidays, in which case the RA will approach within 96 hours). The RA will conduct informed consent procedures with potential participants and obtain written informed consent or verbal consent. Patients being contacted for verbal consent will be contacted twice a week during the two weeks prior to their transplant admission. The RA will follow the verbal consent template and if they are unable to contact the patient, they will leave a voicemail with our study contact information. Patients providing verbal consent will be sent an unsigned copy of the informed consent form for their records. Patients will then be asked to identify a caregiver who might be interested in participating.

Patients without a willing or interested caregiver will still be eligible to participate in the study. The caregiver will be eligible to enroll in the study either at the same time as the patient or within 72 hours after the patient provides written informed consent. We will have a separate consent form for caregivers, which will similarly detail the study procedures. Caregivers will have the option of enrolling in the study in-person with a written informed consent or over the telephone with a verbal consent (Appendix N).

We will follow all the requirements of SOP: Informed Consent Process (CON-100) in obtaining informed consent for study participants.

Patients and caregivers who speak Spanish will have all study procedures and information regarding risks, benefits and study contacts explained to them orally via the use of an interpreter as a first preference, or family member as a second preference. Spanish speaking participants will be given the DF/HCC Spanish consent short form for signing, as well as a copy of the full English consent form for their own reference. Both the Spanish consent short form, and the full English consent form will be signed by the participant, and by a witness. The witness will be either an interpreter or a family member.

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

27.0 Process to Document Consent in Writing

As stated previously, all patients participating in the study will provide written informed consent. Caregivers will have the option of enrolling in the study in-person with a written informed consent or over the telephone with a verbal consent given that the research presents no more than minimal risk of harm [Appendix N].

28.0 Drugs or Devices: not applicable

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

29.0 References

1. Braamse AM, Gerrits MM, van Meijel B, et al: Predictors of health-related quality of life in patients treated with auto- and allo-SCT for hematological malignancies. *Bone Marrow Transplant*, 2011
2. Curtis RE, Rowlings PA, Deeg HJ, et al: Solid cancers after bone marrow transplantation. *N Engl J Med* 336:897-904, 1997
3. Duell T, van Lint MT, Ljungman P, et al: Health and functional status of long-term survivors of bone marrow transplantation. EBMT Working Party on Late Effects and EULEP Study Group on Late Effects. European Group for Blood and Marrow Transplantation. *Ann Intern Med* 126:184-92, 1997
4. Gratwohl A, Baldomero H, Frauendorfer K, et al: EBMT activity survey 2004 and changes in disease indication over the past 15 years. *Bone Marrow Transplant* 37:1069-85, 2006
5. Majhail NS, Mau LW, Chitphakdithai P, et al: National Survey of Hematopoietic Cell Transplantation Center Personnel, Infrastructure, and Models of Care Delivery. *Biol Blood Marrow Transplant* 21:1308-14, 2015
6. Gratwohl A, Baldomero H, Aljurf M, et al: Hematopoietic stem cell transplantation: a global perspective. *JAMA* 303:1617-24, 2010
7. Pidala J, Anasetti C, Jim H: Health-related quality of life following haematopoietic cell transplantation: patient education, evaluation and intervention. *Br J Haematol* 148:373-85, 2010
8. Pidala J, Anasetti C, Jim H: Quality of life after allogeneic hematopoietic cell transplantation. *Blood* 114:7-19, 2009
9. McQuellon RP, Russell GB, Rambo TD, et al: Quality of life and psychological distress of bone marrow transplant recipients: the 'time trajectory' to recovery over the first year. *Bone Marrow Transplant* 21:477-86, 1998
10. Bevans MF, Marden S, Leidy NK, et al: Health-related quality of life in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 38:101-9, 2006
11. El-Jawahri AR, Traeger LN, Kuzmuk K, et al: Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer* 121:951-9, 2015
12. Fife BL, Huster GA, Cornetta KG, et al: Longitudinal study of adaptation to the stress of bone marrow transplantation. *J Clin Oncol* 18:1539-49, 2000
13. Prieto JM, Atala J, Blanch J, et al: Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone Marrow Transplant* 35:307-14, 2005
14. El-Jawahri AR, Vandusen HB, Traeger LN, et al: Quality of life and mood predict posttraumatic stress disorder after hematopoietic stem cell transplantation. *Cancer* 122:806-12, 2016
15. Gemmill R, Cooke L, Williams AC, et al: Informal caregivers of hematopoietic cell transplant patients: a review and recommendations for interventions and research. *Cancer Nurs* 34:E13-21, 2011
16. Fife BL, Monahan PO, Abonour R, et al: Adaptation of family caregivers during the acute phase of adult BMT. *Bone Marrow Transplant* 43:959-66, 2009
17. Siston AK, List MA, Daugherty CK, et al: Psychosocial adjustment of patients and caregivers prior to allogeneic bone marrow transplantation. *Bone Marrow Transplant* 27:1181-8, 2001
18. Foxall MJ, Gaston-Johansson F: Burden and health outcomes of family caregivers of hospitalized bone marrow transplant patients. *J Adv Nurs* 24:915-23, 1996
19. DeFor TE, Burns LJ, Gold EM, et al: A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. *Biol Blood Marrow Transplant* 13:948-55, 2007
20. Syrjala KL, Donaldson GW, Davis MW, et al: Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. *Pain* 63:189-98, 1995

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

21. Syrjala KL, Cummings C, Donaldson GW: Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. *Pain* 48:137-46, 1992
22. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 363:733-42, 2010
23. Temel JSG, J. A. El-Jawahri, A. Pirl, W. F. Park, E. R. Jackson, V. A. Back, A. L. Kamdar, M. Jacobsen, J. Chittenden, E. H. Rinaldi, S. P. Gallagher, E. R. Eusebio, J. R. Li, Z. Muzikansky, A. Ryan, D.P.: Effects of Early Integrated Palliative Care in Patients with Lung and Gastrointestinal Cancer: A Randomized Clinical Trial. *Journal of Clinical Oncology*, in press, 2016
24. Bakitas M, Lyons KD, Hegel MT, et al: Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA* 302:741-9, 2009
25. Zimmermann C, Swami N, Krzyzanowska M, et al: Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 383:1721-30, 2014
26. Dionne-Odom JN, Azuero A, Lyons KD, et al: Benefits of Early Versus Delayed Palliative Care to Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 33:1446-52, 2015
27. McDonald J, Swami N, Hannon B, et al: Impact of early Palliative Care on Caregivers of Patients with Advanced Cancer: Cluster Randomised Trial. *Ann Oncol*, 2016
28. Ferrell BT, JS. Temin, S. Alesi, ER. Balboni, TA. Basch, EM. Firn, JI. Paice, JA, Peppercorn, JM. Phillips, T. Stovall, EL. Zimmermann, C. Smith, TJ.: Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology*, 2016
29. Howell DA, Shellens R, Roman E, et al: Haematological malignancy: are patients appropriately referred for specialist palliative and hospice care? A systematic review and meta-analysis of published data. *Palliat Med* 25:630-41, 2011
30. Manitta VJ, Philip JA, Cole-Sinclair MF: Palliative care and the hemato-oncological patient: can we live together? A review of the literature. *J Palliat Med* 13:1021-5, 2010
31. Epstein AS, Goldberg GR, Meier DE: Palliative care and hematologic oncology: the promise of collaboration. *Blood Rev* 26:233-9, 2012
32. LeBlanc TW, O'Donnell JD, Crowley-Matoka M, et al: Perceptions of palliative care among hematologic malignancy specialists: a mixed-methods study. *J Oncol Pract* 11:e230-8, 2015
33. LeBlanc TW, El-Jawahri A: When and why should patients with hematologic malignancies see a palliative care specialist? *Hematology Am Soc Hematol Educ Program* 2015:471-8, 2015
34. El-Jawahri A, LeBlanc T, VanDusen H, et al: Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA* 316:2094-2103, 2016
35. El-Jawahri A, Traeger L, Greer JA, et al: Effect of Inpatient Palliative Care During Hematopoietic Stem-Cell Transplant on Psychological Distress 6 Months After Transplant: Results of a Randomized Clinical Trial. *J Clin Oncol*:JCO2017732800, 2017
36. Prieto JM, Blanch J, Atala J, et al: Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 20:1907-17, 2002
37. Syrjala KL, Chapko MK, Vitaliano PP, et al: Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning. *Bone Marrow Transplant* 11:319-27, 1993
38. El-Jawahri AR, Vandusen HB, Traeger LN, et al: Quality of life and mood predict posttraumatic stress disorder after hematopoietic stem cell transplantation. *Cancer*, 2015
39. Smith MY, Redd W, DuHamel K, et al: Validation of the PTSD Checklist-Civilian Version in survivors of bone marrow transplantation. *J Trauma Stress* 12:485-99, 1999

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

40. Jacobsen PB, Widows MR, Hann DM, et al: Posttraumatic stress disorder symptoms after bone marrow transplantation for breast cancer. *Psychosom Med* 60:366-71, 1998

41. Jacobsen PB, Sadler IJ, Booth-Jones M, et al: Predictors of posttraumatic stress disorder symptomatology following bone marrow transplantation for cancer. *J Consult Clin Psychol* 70:235-40, 2002

42. Mundy EA, Blanchard EB, Cirenya E, et al: Posttraumatic stress disorder in breast cancer patients following autologous bone marrow transplantation or conventional cancer treatments. *Behav Res Ther* 38:1015-27, 2000

43. Bevans M, Wehrlein L, Castro K, et al: A problem-solving education intervention in caregivers and patients during allogeneic hematopoietic stem cell transplantation. *J Health Psychol* 19:602-17, 2014

44. Jacobsen PB, Le-Rademacher J, Jim H, et al: Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. *Biol Blood Marrow Transplant* 20:1530-6, 2014

45. Mello M, Tanaka C, Dulley FL: Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 32:723-8, 2003

46. DuHamel KN, Mosher CE, Winkel G, et al: Randomized clinical trial of telephone-administered cognitive-behavioral therapy to reduce post-traumatic stress disorder and distress symptoms after hematopoietic stem-cell transplantation. *J Clin Oncol* 28:3754-61, 2010

47. El-Jawahri AL, T.W. Burns, L. J. Denzen, E. Meyer, C. Mau, L. W. Roeland, E. J. Wood, W. A. Petersdorf, E. : What Do Transplant Physicians Think about Palliative Care? A National Survey Study, American Society of Hematology. Atlanta, Georgia, 2017

48. Earle CC, Neville BA, Landrum MB, et al: Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 22:315-21, 2004

49. Tang ST, Wu SC, Hung YN, et al: Determinants of aggressive end-of-life care for Taiwanese cancer decedents, 2001 to 2006. *J Clin Oncol* 27:4613-8, 2009

50. Ho TH, Barbera L, Sashin R, et al: Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. *J Clin Oncol* 29:1587-91, 2011

51. El-Jawahri AL, T. Vandusen, H. Traeger, L. Greer, J.A. Pirl, W.F. Jackson, V.A. Telles, J. Rhodes, A. Spitzer, T.R., McAfee, S. Chen, Y. Lee, SJ. Temel, J.S.: Randomized trial of inpatient palliative care for patients hospitalized for hematopoietic stem cell transplantation (HCT). Americal Society of Clinical Oncology (ASCO) 2016: oral presentation, 2016

52. Irwin KE, Greer JA, Khatib J, et al: Early palliative care and metastatic non-small cell lung cancer: potential mechanisms of prolonged survival. *Chron Respir Dis* 10:35-47, 2013

53. 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

54. Watanabe SM, Nekolaichuk CL, Beaumont C: The Edmonton Symptom Assessment System, a proposed tool for distress screening in cancer patients: development and refinement. *Psychooncology* 21:977-85, 2012

55. Minaya P, Baumstarck K, Berbis J, et al: The CareGiver Oncology Quality of Life questionnaire (CarGOQoL): development and validation of an instrument to measure the quality of life of the caregivers of patients with cancer. *Eur J Cancer* 48:904-11, 2012

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

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

58. Santana MJ, Au HJ, Dharma-Wardene M, et al: Health-related quality of life measures in routine clinical care: can FACT-fatigue help to assess the management of fatigue in cancer patients? *Int J Technol Assess Health Care* 25:90-6, 2009

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

59. Carver CS: You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med* 4:92-100, 1997

60. Sorror ML, Maris MB, Storb R, et al: Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 106:2912-9, 2005

61. Armand P, Kim HT, Logan BR, et al: Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood* 123:3664-71, 2014

62. Glickman ME, Rao SR, Schultz MR: False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol* 67:850-7, 2014

63. Nipp RD, Greer JA, El-Jawahri A, et al: Age and Gender Moderate the Impact of Early Palliative Care in Metastatic Non-Small Cell Lung Cancer. *Oncologist* 21:119-26, 2016

64. Little RJA, Rubin DB: Statistical analysis with missing data (ed 2nd). Hoboken, N.J., Wiley, 2002

65. Dempster AP, Laird NM, Rubin DB: Maximum Likelihood from Incomplete Data Via EM Algorithm. *Journal of the Royal Statistical Society Series B-Methodological* 39:1-38, 1977

66. Demidenko E: Mixed models : theory and applications with R (ed Second edition.). Hoboken, New Jersey, Wiley, 2013

67. Hogan JW, Laird NM: Model-based approaches to analysing incomplete longitudinal and failure time data. *Stat Med* 16:259-72, 1997

68. Daniels MJ, Hogan JW: Missing Data in Longitudinal Studies Strategies for Bayesian Modeling and Sensitivity Analysis, Chapman & Hall/CRC Monographs on Statistics & Applied Probability. Hoboken, Taylor and Francis,, 2008, pp 1 online resource (324 p.)

PROTOCOL TITLE: Multi-Site Randomized Trial of Inpatient Palliative Care for Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

