Appendix A: Protocol Documents

1) **Study protocol along with statistical plan**

2) **Summary of Protocol Amendments**

Study Protocol:

Randomized Trial of a Collaborative Palliative and Oncology Care Model for Patients with Acute Myeloid Leukemia

Lead Site:

Massachusetts General Hospital (Boston, MA)

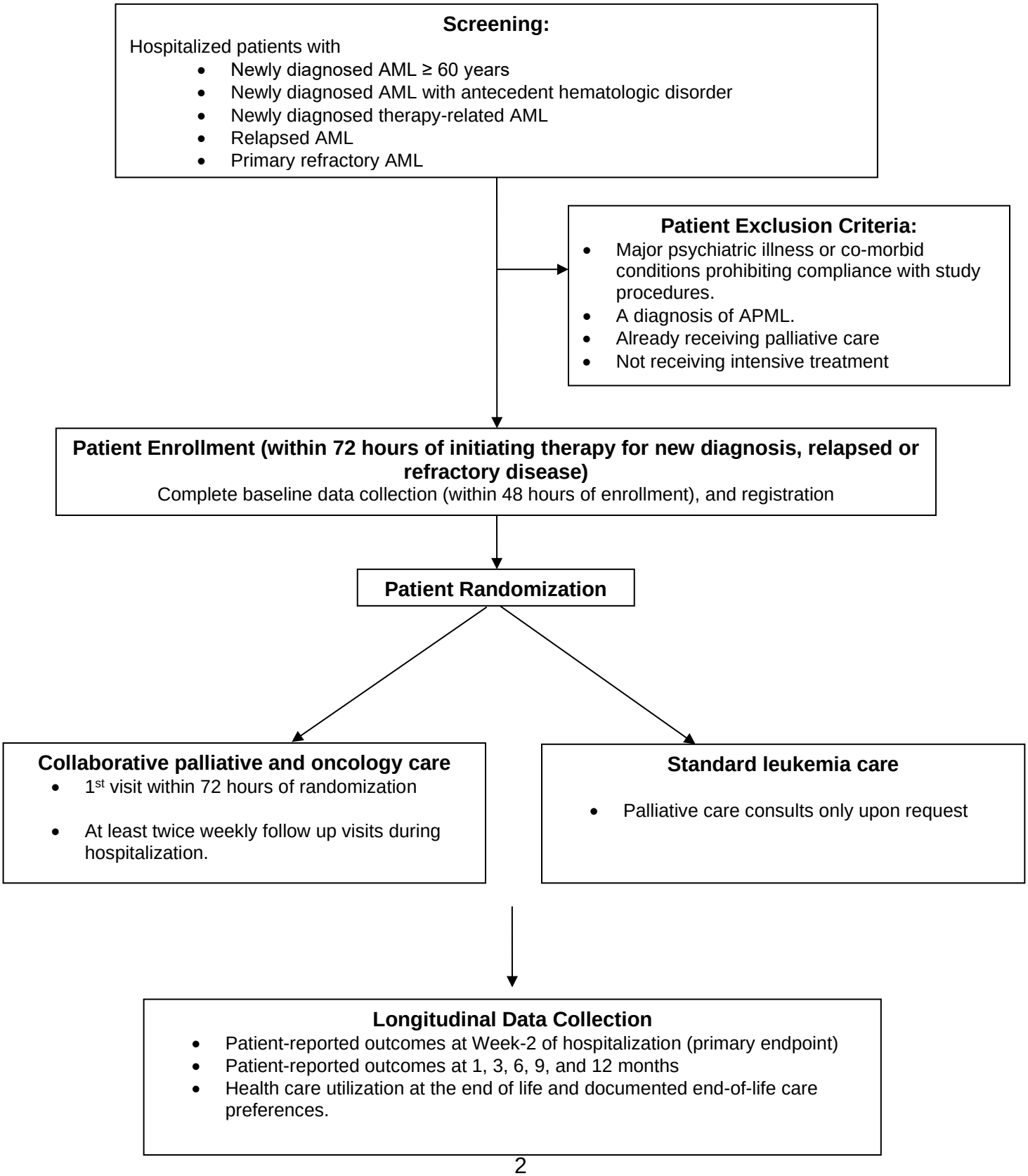
Participating Site(s):

Duke Cancer Center (Durham, NC)

The Hospital at the University of Pennsylvania (Philadelphia, PA)

The Ohio State University Comprehensive Cancer Center (Columbus, OH)

SECTION I: Protocol Schema



SECTION II: BODY OF PROTOCOL

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1 INTRODUCTION

1.1 Overview

Acute myeloid leukemia (AML) is a common hematologic malignancy, and is the sixth leading cause of cancer-related death in the United States. Therefore, addressing the needs of patients with AML at the end of life (EOL) is critically important. Early integration of palliative and oncology care for patients with advanced solid tumors has been shown to improve quality of life (QOL) and mood, reduce symptom burden, and decrease health care utilization at the EOL. However, these advances have not impacted the care of patients with AML. In fact, patients with AML experience substantial physical and psychological symptom burden, which results in significant deterioration in their QOL and mood. Moreover, while the majority of cancer patients express a strong preference to die at home and minimize time spent in the hospital at the EOL, patients with AML are often hospitalized during the last month of life, receive intensive therapies at the EOL, and frequently die in the hospital. Therefore, interventions are critically needed to improve QOL and the delivery of high-quality EOL care for patients with AML.

While palliative care clinicians are increasingly asked to care for patients with solid tumors, they are rarely consulted to assist in the management and support of patients with AML. Cultural barriers and misconceptions have contributed to the lack of collaboration with palliative care services in the care of patients with leukemia. However, palliative care clinicians are experts in managing complex symptoms, enhancing patients' prognostic understanding, eliciting EOL care preferences, and engaging patients in EOL decision-making. Thus, palliative care clinicians are ideally suited to address the challenging symptoms and unmet needs for patients with AML at the EOL.

We recently completed a randomized study of integrated inpatient palliative care versus standard transplant care alone in patients with hematologic malignancy undergoing hematopoietic stem cell transplantation (HCT), and observed significant improvements in patients' QOL, symptom burden, depression, and anxiety during hospitalization for HCT. This proof-of-concept study established both the feasibility and potential efficacy of integrating palliative care in improving outcomes for patients with hematologic malignancy. We now seek to define the role of palliative care in optimizing the quality of life and EOL care of hospitalized patients with high-risk AML.

We propose to conduct a randomized controlled trial of collaborative palliative and oncology care versus standard leukemia care alone in hospitalized patients with high-risk AML. The intervention will entail inpatient longitudinal palliative care visits for patients with AML focusing on symptom management, illness understanding, treatment decision-making, EOL care planning, and patients' coping. In this project, we will evaluate the impact of the intervention on 1) QOL and symptom burden; 2) EOL care discussions and documentation of EOL care preferences; and 3) health care utilization at the EOL. Serving as the foundation for a larger multi-site trial, this research will benefit the field of oncology by demonstrating improvements in the quality of care and resource utilization through timely integration of palliative care for hospitalized patients with high-risk AML.

1.2 Background and rationale

Patients with AML confront a life-threatening illness that requires intensive therapies and frequent hospitalizations

AML is an aggressive hematologic malignancy characterized by an abrupt onset, an urgent need to initiate intensive chemotherapy, and a relatively poor prognosis with significant risk of relapse.[1-3] Upon diagnosis, patients learn that they have a life-threatening illness requiring immediate prolonged hospitalization to receive intensive chemotherapy.[1-3] Moreover, patients often endure frequent additional hospitalizations for infectious complications which can include receipt of further chemotherapy, especially at the time of disease relapse.[1-4] Notably, the receipt of intensive chemotherapy is associated with significant toxicities and potentially life-threatening complications such as bleeding and sepsis.[5-8] Thus patients with AML

confront an unexpected and immediate threat to their life, as well as long and difficult hospitalizations associated with significant side effects and potential for serious complications.

Patients with AML endure substantial physical and psychological symptom burden

During therapy, patients with AML experience substantial physical symptoms which negatively impact their functioning and QOL.[6,9-11] Common symptoms during hospitalization include fever, fatigue, pain, insomnia, mucositis, nausea, vomiting, and diarrhea.[5-8] Psychological symptoms are also prominent in this population, and are related to extensive physical and psychological morbidity.[10,12] Over one third of patients experience acute stress reactions due to the initial shock of the diagnosis and the immediate life disruptions including urgent need for hospitalization.[13,14] During hospitalization, patients experience physical and social isolation and a sense of loss of control, they mourn their personal losses and struggle with the uncertainty of their prognosis, which leads to hopelessness, depression, and anxiety.[5-8],[13-17] We conducted a prospective longitudinal study of patients with AML which demonstrate that patient experience a dramatic increase in depression symptoms and psychological distress and decline in QOL during hospitalizations and throughout their illness course. Importantly, the psychological sequelae during hospitalizations can have long-lasting impact on patients' QOL, mood, and long-term adaptation to their illness. Therefore, addressing the physical and psychological needs of hospitalized patients with AML has the potential to substantially improve their outcomes, both during hospitalization and in the long term.

There is a critical need to optimize EOL care in patients with AML

As AML represents the sixth leading cause of cancer-related death in the US, addressing the needs of these patients at the EOL is critically important.[18] In addition to the substantial physical and psychological symptom burden patients experience throughout their illness course, studies suggest that patients with AML may not be receiving high-quality EOL care.[19,20] While most cancer patients express a strong preference to die at home and minimize time spent in the hospital at the EOL, patients with AML are often hospitalized during the last month of life, and frequently die in the hospital. Moreover, many die in the intensive care unit and receive chemotherapy during the last month of life. Thus, patients with AML represent a uniquely vulnerable population with tremendous unmet palliative and EOL care needs, and they frequently receive aggressive care at the EOL.

When it comes to EOL decision-making, patients with AML are confronted with challenging decisions, balancing the risk and benefits of aggressive therapies that offer an uncertain chance of cure.[10,21] Often patients are faced with the dilemma of sacrificing their QOL and spending a significant proportion of their time in the hospital to pursue potentially curative therapy such as high dose chemotherapy and stem cell transplantation.[22] This prognostic uncertainty and highly variable course for patients with AML makes it difficult to identify points along the disease trajectory to target interventions which ensure the delivery of high-quality EOL care. [17,-18, 22] The potential for curative therapy for many patients with AML may make EOL discussions seem unnecessary. However, as the sixth leading cause of cancer related mortality, communication about EOL care preferences is undeniably relevant to these patients. Unfortunately, data suggest that patients with AML are not engaging in timely discussions with clinicians about their EOL care goals and preferences, and consequently receive aggressive care at the EOL. [18,22]

A recent Institute of Medicine (IOM) report, "Dying in America," described marked inadequacies in the care of patients at the EOL, highlighting substantial deficiencies in communication and advance care planning.[23] One of their key recommendations was that clinicians integrate high-quality conversations about EOL care preferences into the longitudinal care of patients with serious illness, and that discussions are clearly documented in the health record.[23] Since previous research has shown that patients with AML receive aggressive medical are care the EOL, it is imperative that we conduct studies to improve the delivery of EOL care for this vulnerable population.[22]

Palliative care is ideally suited to address the complex physical, psychological, and EOL care needs of patients with AML

The American Society of Clinical Oncology (ASCO) released a provisional clinical opinion in 2012 recommending concurrent palliative care from the time of diagnosis for all patients with metastatic cancer and/or high symptom burden.[24] This recommendation is based on several studies demonstrating improvements in QOL and symptom burden, and a decrease in health care utilization at the EOL for patients with advanced solid tumors receiving early palliative care.[25-28] Specifically, early integration of palliative care leads to improvement in patients' prognostic understanding, higher documentation of patients' EOL care preferences, and early referrals for hospice services.

While we have made significant progress in improving clinical outcomes at the EOL for patients with solid tumors,[25,29] these advances have not impacted the care of patients with AML despite the tremendous physical, psychological, and EOL care burden experienced by this population. In fact, patients with AML rarely utilize palliative care or hospice services.[20,30] Cultural barriers and misconceptions have contributed to the lack of collaboration with palliative care services in the care of patients with AML. However, palliative care clinicians are experts in managing complex symptoms and thus may be helpful in treating the challenging toxicities experienced by hospitalized patients with AML. Additionally, given the benefits of integrated palliative care in improving patients' prognostic understanding and EOL care discussions, palliative care clinicians would provide essential expertise in improving EOL communication, addressing prognostic uncertainty, and enhancing patient-centered EOL decision-making in AML.

Rationale for the proposed collaborative palliative and leukemia care model for hospitalized patients with high-risk AML

We recently completed a randomized study of integrated palliative care versus standard oncology care alone in patients with hematologic malignancies (37% with acute leukemia) receiving intensive chemotherapy and stem cell transplantation.[31] The palliative care clinicians focused on several domains including addressing physical and psychological symptoms, managing patient's expectations, and enhancing their coping. Patients randomized to the intervention reported significant improvements in their QOL, symptom burden, depression, and anxiety during transplant hospitalization compared to those randomized to the control arm. This proof-of-concept study established both the feasibility and potential efficacy of integrating palliative care during hospitalization for patients with hematologic malignancies undergoing intensive therapies such as stem cell transplantation. Since hospitalized patients with AML report similar physical and psychological symptoms as those receiving high dose chemotherapy and stem cell transplantation, they are likely to benefit from inpatient palliative care integration to reduce their symptom burden and improve the quality of their care.

We have also conducted two randomized trials of palliative care integrated with standard oncology care for patients with newly diagnosed incurable solid tumors.[25] The palliative care intervention focused on symptoms, patient coping, illness understanding, and EOL decision-making. These studies have also shown improvement in patient-reported outcomes, increase in EOL discussions, and a decrease in health care utilization at the EOL.[25,32] These studies have established the role of palliative care in optimizing EOL care for patients with advanced cancer. Thus, patients with AML may benefit from palliative care integration to facilitate EOL discussions and improve EOL outcomes.

Given our expertise in conducting randomized trials of longitudinal palliative care interventions for patients with cancer, we now propose a collaborative palliative and leukemia care intervention for patients with high-risk AML. We have focused on patients with high-risk disease given the poor prognosis of this population and the critical need to address their EOL care needs. The proposed palliative care intervention will focus on 1) managing symptoms, setting up appropriate expectations, and enhancing patient's coping during hospitalizations - building upon our experience with the palliative care intervention in patients with hematologic malignancies; 2) addressing illness understanding and enhancing EOL communication - building upon our experience with the palliative care interventions in solid tumor patients.

We propose to conduct a multi-site randomized trial of a collaborative palliative and leukemia care model compared to standard leukemia care alone for patients with high-risk AML. We will test the efficacy of the

palliative care intervention in improving patient-reported outcomes and enhancing EOL care for this population.

2 OBJECTIVES

1. **To determine the impact of collaborative palliative and leukemia care integrated with standard leukemia care on QOL and symptom burden in patients with high-risk AML.**

Hypothesis: Patients randomized to the palliative care intervention will report improved QOL and lower physical and psychological symptoms compared to those receiving leukemia care alone.

2. **To assess the impact of collaborative palliative and leukemia care integrated with standard leukemia care on EOL discussions and documentations of EOL care preferences for patients with AML.**

Hypothesis: Compared to patients receiving standard leukemia care, those randomized to the intervention will be more likely to discuss their EOL care preferences with their clinicians and have their EOL care preferences documented in the health record.

3. **To assess the effect of collaborative palliative and leukemia care integrated with standard leukemia care on health care utilization at the EOL for hospitalized patients with high-risk acute AML.**

Hypothesis: Compared to patients receiving standard leukemia care, those randomized to the intervention will 1) receive less chemotherapy in the last 30 days of life; 2) have fewer hospitalizations during the last 30 days of life; and 3) are more likely to utilize hospice care and have longer hospice length-of-stay at the EOL.

3 RESEARCH SUBJECT SELECTION

We will recruit 160 consecutive hospitalized patients with high-risk AML receiving intensive treatment at three sites. Massachusetts General Hospital (MGH) is considered the lead and sponsor site of the study, with Duke Cancer Center, the Hospital at the University of Pennsylvania (UPenn), and Ohio State University as participating sites. We have focused on enrolling hospitalized patients with high-risk disease given the high symptom burden these patients experience during hospitalization, and the potential benefits from involvement of palliative care in a higher-risk cohort in terms of the need to enhance communication about EOL care. Intensive treatment will be defined as one of the following chemotherapy regimens which require a 3-6 week hospitalization, including 1) a combination of anthracycline and cytarabine “7+3” or modification of this regimen on a clinical trial with an additional drug added to the “7+3” backbone; 2) other similar intensive chemotherapy regimens requiring 3-6 week hospitalization. While other patients with AML would also likely benefit from earlier involvement of palliative care, we have included a patient target audience who has the greatest potential to achieve the goals of the established proposal.

Patient Eligibility Criteria:

1. Hospitalized patients with high-risk AML, defined as:
    a. Newly diagnosed patients with AML ≥ 60 years of age
    b. Newly diagnosed AML with antecedent hematologic disorder
    c. Newly diagnosed therapy-related AML
    d. Relapsed AML
    e. Primary refractory AML

Patient Exclusion criteria:

1) Patients already receiving palliative care
2) Major psychiatric illness or comorbid conditions prohibiting compliance with study procedures as determined by the treating oncologist.
3) A diagnosis of acute promyelocytic leukemia (APML)
4) Patients receiving non-intensive treatment

4 RESEARCH SUBJECT ENTRY

4.1 Study research subject entry

All participating sites have an admission log which includes a list of all patients with acute leukemia admitted to the hospital. This log is updated daily and the leukemia teams at all three institutions have agreed to give study staff access to the log to screen patients for study particpiation. Study staff will review the daily leukemia admission logs to screen for eligible patients. Our screening methods will ensure we identify all patients who are eligible for study participation.

We will use identical recruitment and enrollment procedures used in our prior randomized trial of inpatient palliative care integrated with transplant care. Once a potentially eligible patient is identified, the research coordinator will send an email to the leukemia clinician to notify them that their patient is eligible for study participation, and inquire about any concerns regarding their participation. If the clinicians have objections to their patients' participation in the study, we will document the reason and not approach those individuals. If the leukemia clinicians have no objections, the study staff will approach patients for study participation within 72 hours of initiating therapy for their new diagnosis or diagnosis of relapsed or refractory disease (excluding public holidays, in which case staff will approach in 96 hours). The research coordinator will review the consent form with potential particpiants, which will clearly detail the nature of the study procedures, the time requirements, and the frequency of the self-report questionnaires. The research coordinator will obtain written informed consent from the participant and provide them with a copy of the signed consent form. From the intiation of new therapy, potentially eligible patients will have 72 hours (excluding public holidays) to consider enrollment.

Study participants will complete baseline self-report assessments at the time of obtaining informed consent for the study (within a 48-hour window). If patients sign the consent form, but do not complete baseline, they will be excluded from the study. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

4.2 Registration and randomization procedures

Patients who provide informed consent will complete baseline study measures. After administration of baseline questionnaires, patients from all sites will be registered centrally with the DF/HCC Office of Data Quality (ODQ) central registration system. The ODQ office will be responsible for randomization of study participants. Randomization will be computer-generated and stratified by study site and disease status (newly diagnosed vs. relapsed disease). Registration Process for DF/HCC Institutions DF/HCC Standard Operation Procedure for Human Subject Research Titled Subject Protocol Registration (SOP#: REGIST-101) must be followed. For each study participant, we will complete the following registration procedures:

- We will obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- We will complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Only eligible participants will be registered. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in this protocol and reflected on our eligibility checklist.**
- We will fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295.
- The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.
- An email confirmation of the registration and/or randomization will be sent to the Overall Principal Investigator (PI), study coordinator(s) from the Lead Site, treating investigator and registering

person immediately following the registration and/or randomization.

***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.

4.3 Registration process for external investigative sites

To register a participant, the following documents should be completed by the external site research team and faxed or emailed to the MGH lead study coordinator [fax 617-643-5843; email aljankowski@mgh.harvard.edu]:

- Signed and de-identified participant consent form
- HIPAA authorization form
- Completed eligibility checklist

The research study staff at the participating site will then call or email the MGH lead study coordinator to verify eligibility [617-643-4016; aljankowski@mgh.harvard.edu]. To complete the registration process, the MGH lead study coordinator 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. The coordinator will fax or e-mail the participant study number, and randomization assignment to the participating site.

5 STUDY DEISGN AND METHODS

5.1 Design and study type

The proposed project is a multi-site prospective randomized study evaluating the efficacy of a collaborative palliative and leukemia care versus standard leukemia care in 160 hospitalized patients with high-risk AML. Randomization will be stratified by study site and disease status (newly diagnosed vs relapsed or refractory).

5.2 Selection of instruments

Study instruments were selected based on their appropriateness for measuring the major outcomes of palliative care. All measures were used in our past palliative care interventions and demonstrate strong psychometric properties. All measures are valid, reliable, and frequently used within cancer patient populations.

Study staff will administer study assessments at baseline, week-2 during hospitalization (+/- 3 day window), and at 1, 3, 6, 9, and 12 months (+/- 7 day window) from the time of enrollment. The demographic questionnaire 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 participants 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.

- **Demographic questionnaire:** Participants will self-report their age, sex, race/ethnicity, marital status, religion, and education level, and relationship status, and living situation. [Appendix A]

- **QOL (Patient):** We will use the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leuk) to assess QOL.[33] The FACT-Leuk assesses physical, social/family, emotional, and functional well-being (27 items) and leukemia- specific symptoms (17 items) over the past 7 days.[34] [Appendix B]
- **Symptom burden:** We will administer the revised Edmonton Symptom Assessment Scale (ESAS) to assess various symptoms relevant to this population.[36] [Appendix C]
- **Mood:** We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety in all study participants. The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week.[37] [Appendix D] We will also use the PHQ-9, 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.[38] [Appendix E]
- **Post-traumatic stress:** We will use the Post-Traumatic Stress Disorder Checklist (PCL) Civil Version, 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 F]
- **Brief Cope:** The Brief Cope is a 28-item questionnaire that assess 14 methods of coping (e.g., self-distraction, humor, denial) using a 4-point Likert scale ranging from 1 "a lot" to "never".[39] [Appendix G]
- **Patient-reported EOL care preferences discussion:** We will use one item to assess patient-report of discussing EOL care with their clinician "Have you and your doctors discussed any particular wishes you have about the care you want to receive if you were dying?"[40] [Appendix H]

Data collected from the health care record: Clinical, disease, and treatment characteristics will be collected at baseline including: ECOG Performance Status, clinical comorbidities as measured by the Charlson Comorbidity Index,[41] underlying diagnosis, date of diagnosis, disease risk based on the Disease Risk Index,[42] cytogenetics and molecular markers, and hospital length-of-stay. We will also collect data on additional treatments including consolidation chemotherapy and/or hematopoietic stem cell transplantation. We will also collect information on the incidence of relapse, death dates, documented EOL care preferences (code status), and EOL health care utilization including hospitalizations, chemotherapy administration, intensive care unit admissions, and hospice referrals. EOL outcomes will be collected up to 5 years from study enrollment.

5.3 Description of Intervention

5.3.1 Palliative care clinician training

Given heterogeneity in palliative care practices, all participating palliative care clinicians will undergo training to ensure that the provision of palliative care services is consistent across study sites. Our research team has developed the palliative care intervention guide based on our prior studies examining the QOL and physical and psychological symptom burden of patients with AML. We refined the intervention guide after conducting qualitative interviews with the palliative care and leukemia clinicians [Appendix I, Collaborative Palliative and Leukemia Care Intervention Guide]. 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, management of expectations, or illness understanding) is dependent on each patient's course during their illness. However, it does provide guidance for palliative care clinicians about addressing each content area, when appropriate during the patients' course. Prior to the study start, all participating palliative care clinicians will attend a full-day training using video conferencing to review the intervention guide.

5.3.2 Palliative care intervention

Patients randomized to the palliative care intervention will receive collaborative care from palliative care and leukemia for the remainder of their illness. After providing informed consent, patients will have their first palliative care intervention visit within 72 hours during their hospitalization (excluding public holidays). At the initial visit, the palliative care clinician will focus on establishing rapport, assessing needs, and developing a relationship with the patient. During subsequent visits, the palliative care clinician will focus on addressing patients' symptoms, assessing their illness understanding, ascertain their goals and

expectations, and assist with treatment decision-making. The palliative care clinician will also identify points during the illness course to discuss the patients' preferences for care at the EOL and educate them about the role of hospice services. During the inpatient course, palliative care clinicians will follow the patients longitudinally during their hospitalization and will see them at least twice per week. Palliative care clinicians will continue to follow patients longitudinally during subsequent hospitalizations. The palliative care intervention is primarily an inpatient intervention. However, patients, palliative care or leukemia clinicians may ask for outpatient palliative care follow-up, as needed. Furthermore, patients, palliative care and leukemia clinicians may initiate additional inpatient visits as needed.

The palliative care clinicians will document all visits with intervention participants in the electronic medical record. They will also communicate their recommendations directly to the inpatient leukemia team in-person or via telephone. Moreover, palliative care and leukemia clinicians may contact one another regarding intervention patients at their discretion throughout the study period.

5.3.3 Standard leukemia care alone (control arm):

Patients randomized to the standard leukemia care arm will not meet with palliative care clinicians, though they may consult with palliative care at their request or at the discretion of their treating clinicians. In most leukemia units across the country (including at participating sites), palliative care is consulted in less than 5% of patients hospitalized with AML, and therefore we anticipate minimal cross contamination in this study. At most cancer centers, supportive care measures are instituted at the discretion of the leukemia 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. Patients randomized to standard leukemia care will receive all supportive care measures as instituted by the leukemia team including social work consultations upon request.

5.4 Data collection

Table 1: Data Collection Timeline

	Baseline	Week-2 during hospitalization	1, 3, 6, 9, and 12 months	After death
Patient Measures:				
Demographic Questionnaire	**X**			
FACT-Leuk	**X**	**X**	**X**	
ESAS	**X**	**X**	**X**	
HADS	**X**	**X**	**X**	
PHQ-9	**X**	**X**	**X**	
Brief Cope	**X**	**X**	**X**	
PCL (PTSD)	**X**	**X**	**X**	
Patient-report EOL care discussion preference			**X*** *Excludes month 1 timepoint	
Outcomes collected health record				
Documented EOL care preferences				**X**
Dates of chemotherapy				**X**
Dates of hospitalization				**X**
Dates of emergency department visits				**X**
Dates of intensive care unit admissions				**X**
Date hospice referral				**X**

5.5 Description of study process

5.5.1 Instrument administration

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

Participants will use tablet computers to complete questionnaires 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. Participants who are not present in the hospital or clinic during the period of data collection will be provided with remote access to the REDCap system or paper-based questionnaires for home administration. If participants 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. The study team will contact patients daily for two days to remind them to complete and return the surveys. If study participants fail to complete the surveys within the timeframe for the expected time point, we will report the data as missing and document the reason for incompletion. Table 1 details the schedule for administering the self-report measures. All participants will complete baseline assessments within 48 hours of study enrollment. All participants will then have a second evaluation at two weeks from enrollment (+/- 3 day window) and at 1, 3, 6, 9, and 12 months (+/- 7 day window) from the time of enrollment.

In addition, we will abstract patient data from the electronic health record (see section 5.2). We will collect the following data: (1) documentation of EOL care preferences, (2) dates of chemotherapy administration, (3) dates of emergency department visits, (4) dates of hospitalization, (5) dates of intensive care unit admissions, and (4) date of hospice referral. This data will be abstracted throughout the trial and until a patient's death and directly imputed into REDCap.

5.5.2 Intervention administration

Patients randomized to the palliative care intervention will meet with the palliative care clinicians on the inpatient setting within 72 hours after study randomization (excluding public holidays). After the initial visit, the palliative care team will follow patients longitudinally during their hospitalization and will see them at least two times per week on the inpatient setting. Palliative care will also follow patients longitudinally on subsequent hospitalizations and will see them at least twice per week. Outpatient palliative care will be available to see patients if requested by the patient, leukemia or palliative care clinicians. Patients, palliative care or leukemia clinicians may initiate additional visits as needed.

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

5.5.3 Special concerns

We do not anticipate any complications during the proposed study because all intervention procedures are occurring while the patient is in the direct care of their treating oncologist and/or a palliative care clinician who are trained in responding to any psychological or physical complication that may occur. We have administered these patient-reported assessments to over 200 patients in previous studies and there have been no complications.

Research teams at participating sites will meet every other week throughout the study period, and will discuss any issues or concerns that may arise regarding the study procedures. Should the protocol require modifications or amendments based on these meetings, the overall Principal Investigator will

make the necessary changes and submit them to the DF/HCC IRB for approval. Once approved by the DF/HCC IRB, the amendment will be submitted to external site IRBs.

5.5.4 Compensation
We will provide no patient or clinician compensation for participating in this study.

5.6 Adverse reactions and their management
No adverse reactions are anticipated during the proposed study as a result of the study procedures.

5.6.1 Reporting adverse or unanticipated Events
While no adverse or unanticipated events are expected in this behavioral trial, any such events will be immediately reported to the IRB. There is minimal chance of causing harm with this study. We have administered all of the questionnaires to over 200 patients in previous studies with no adverse events. While some items on the questionnaires are sensitive in nature, no previous study participants have withdrawn from prior studies due to the questionnaires..

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

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

5.6.3 Reaction management
Should participants experience distress; the inpatient or outpatient leukemia social worker will be contacted to see the participant. All inpatient and outpatient staff are familiar with how to contact the social worker via pager. The leukemia social workers at MGH have all agreed to be available to respond and help with the management of any adverse reactions.
If participants report suicidal ideations during the interview or while completing any of the questionnaires, the research team will inform study participants that there is an obligation to inform their oncologist and the leukemia social worker. The oncologist and social worker will then determine the need to involve psychiatry and take further action as deemed necessary.

6 ETHICAL AND LEGAL ISSUES

6.1 Confidentiality
All patient information will remain confidential and stored on Partners computers and in REDCap. Identifiers such as name will only be used during the initial data retrieval process and can be destroyed once all data records have been obtained and data analysis completed.
Participants' response to survey questions will remain confidential unless there are active suicidal ideations confirmed by the research team. Under these circumstances, as clearly stated in the patient consent form, participants will be informed that the research team has a formal obligation to inform the oncologist and the leukemia social worker due to concern for participants' safety. The oncologist and the social worker will then determine the need to involve psychiatry and/or take further action as deemed necessary.

Patient data will be collected at each institution using RedCap. Each site will maintain their own separate list of patient names and study IDs. Participants will be identified on study forms and in the REDCap database by participant number only. To further prevent the loss of confidentiality, all electronic information stored on the main database within the MGH is password protected, and is protected by anti-virus software. Only study staff will have access to the study data on Shared file areas. At the completion of the study, a de-identified data file will be transferred from external sites to the MGH lead site using a secure data transfer.

7 STATISTICAL ANALYSIS

7.1 Primary and secondary endpoints

Primary endpoint: The primary endpoint is comparison of the change in patients' FACT-Leukemia score from baseline to week-2 between study arms.

Secondary endpoints

1. Compare FACT-Leukemia scores longitudinally between the study arms.
2. Compare depression and anxiety symptoms (HADS, and PHQ-9) longitudinally between the two arms.
3. Compare symptom burden (as per ESAS) longitudinally between study arms.
4. Compare patient-reported PTSD (as per PCL) longitudinally between study arms.
5. Compare patient-report of discussion EOL care preferences between study arms using the following item: "have you and your doctors discussed any particular wishes you have about the care you would want to receive if you were dying?"[40] Although patients will complete this measure repeatedly during the course of the study, we will use the final assessment either prior to death or at one year follow-up (whichever comes first for this analysis.
6. Compare rates of documentation of EOL care preferences (i.e. code status yes documented vs. no) in the electronic health record between the two study arms within 30 days of death.
7. Compare rates of chemotherapy at the end of life between the two study arms
8. Compare rates of hospitalizations at the end of life between the study arms
9. Compare rates of hospice utilization and length-of-stay in hospice at the EOL between the study arms.

7.2 Sample size and statistical power or precision associated with the sample size. The length of time required to accrue an adequate number of subjects to the study should be indicated.

Study participants will be recruited over a 15-month period at participating sites. Although, we observed a large effect size for our palliative care intervention on patient-reported QOL during hospitalization for hematopoietic stem cell transplantation (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 a novel population of patients with AML, the assessment of long-term 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 = 12) in QOL from baseline to week-2 between intervention and control group. With a sample size of 160, we will have 93% power to detect at least 6.9 point difference in change in patient QOL from baseline to week-2 between groups using a two-sample t-test 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-transplant in our prior study. With a sample size of 160, 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 4.3 point difference in patient-reported QOL at 3 and 6 months between the two groups (based on the difference we detected at 3 months in our previous study).

7.3 Stratification factors and intervention allocation plan for randomized studies.

Patients will be randomized in 1:1 fashion between study arms with stratification based on the following factors: 1) study site, and 2) disease status (newly diagnosed vs. relapsed/refractory disease).

7.4 Stratification factors and their impact on design.
Stratification factors do not impact the design of the study, but will be considered during data analysis to compare baseline statistics and outcomes based on initial eligibility criteria to participate in the study. Post-hoc comparisons between newly diagnosed patients and those with relapsed/refractory disease will determine if different outcomes existed between these two groups.

7.5 Early stopping rules, if appropriate.
Not applicable. Participants will be included in the study as long as they continue seeking care at the study sites. Death or discontinuation of clinic visits are the only reasons for participants to not be included in the full intervention.

7.6 Definition of and allowance in design for unevaluable/ineligible participants.
No unevaluable and/or ineligible participants will be included in this study.

7.7 Analysis plan
Hypothesis 1: Patients randomized to the palliative care intervention will report improved QOL and lower physical and psychological symptoms compared to those receiving leukemia care alone.
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. The primary endpoint of the study will be to compare patient QOL (FACT-Leuk) scores at week-2 between the study groups using Analysis of Covariance (ANCOVA) controlling for baseline values and demographic and clinical factors (as necessary for any imbalances in baseline variables). We will also compare changes in symptoms (ESAS), depression and anxiety symptoms (HADS and PHQ9), post-traumatic stress (PCL) from baseline to week-2 between the study groups using ANCOVA models controlling for baseline values and demographic and clinical factors (as necessary for any imbalances in baseline variables) to assess the effect of the intervention on all outcomes. In the event that the effect of the intervention differs by disease status or other patient characteristics, we will examine these variables as interaction terms in the ANCOVA analyses. We will also compare the rates of psychological distress between study groups at week-2. We will transform the HADS score into a dichotomous outcome with categories reflecting the presence of absence of clinically significant depression and anxiety. We will then calculate Fisher's exact tests to assess the association between study group and presence of depression/anxiety, using risk difference and relative risk to compare proportions between the two groups. We will similarly dichotomize the PHQ-9 scores and analyze the data using the Fisher's exact test.

We will also compare QOL (patient: FACT-Leuk), mood (HADS and PHQ-9), symptom burden (ESAS), and patients' post-traumatic stress disorder (PCL) longitudinally using 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.

Hypothesis 2: Compared to patients receiving standard leukemia care, those randomized to the intervention will be more likely to discuss their EOL care preferences with their clinicians and have their EOL care preferences documented in the health record.
We will examine patient report of discussing EOL care preferences with their clinician using the following item: "Have you and your doctors discussed any particular wishes you have about the care you want to receive if you were dying?"[40] Although patients complete this measure repeatedly during the course of the study, we will use the final assessment either prior to death or at 12 months follow-up (whichever comes first) for this analysis. We will examine differences in intervention and control arms in the rate of

patients reporting "yes" to this item, first with a two-sided Fisher's exact test and then with logistic regression models adjusting for any covariates that are potentially imbalanced between the two groups at baseline. To examine differences in rates of documentation of EOL care preferences, including designated code status, we will first conduct two-sided Fisher's exact test and then logistic regression adjusting for any relevant covariates that differ between groups at baseline.

Hypothesis 3: Compared to patients receiving standard leukemia care, those randomized to the intervention will 1) receive less chemotherapy in the last 30 days of life; 2) have fewer hospitalizations during the last 30 days of life; and 3) are more likely to utilize hospice care and have longer hospice length-of-stay at the EOL.

To test differences in rates of chemotherapy administration and hospitalizations, and hospice utilization during the last 3, 7, 14, and 30 days of life between patient groups, we will use two-sided Fisher's exact test with follow-up logistic regression analyses adjusting for covariates that are imbalanced between groups. To assess differences in the number of days receiving hospice care, we will use the Wilcoxon rank-sum test, followed by Poisson regression adjusting for any imbalances in patient or clinical characteristics. For these EOL care outcomes, we will examine all deceased patients by the end of the study period.

Exploratory analyses: We will conduct bootstrapped tests of mediation to determine whether group differences in patient-reported QOL (FACT-Leuk) are mediated by improved symptom burden (mediator: ESAS), 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.[43] We will create interaction terms for the ANCOVA analyses and linear mixed models to examine whether differences in patient-reported QOL are moderated by patient factors (age, gender, race), or disease and treatment factors (disease status, chemotherapy intensity).

7.8 Handling of missing data in the analysis.

The analyses will initially focus on the study completers to estimate the effect of the collaborative palliative care intervention in hospitalized patients with high-risk AML 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 methods. However, if we find that participants do not complete the study because of disease worsening, suggesting missing data are not random, we will employ maximum likelihood estimate from incomplete data, or terminal decline joint modeling approach[44] under the direction of our biostatistician, Dr. Shuli Li.

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Summary of Protocol Amendments

1) **Amendment 1 12/2016:** Modification of study assessments to reduce participant burden by removing the FACT-Fatigue measure from all study assessments.

2) **Amendment 2 2/2017:** Modification of eligibility criteria to explicitly exclude patients receiving non-intensive treatment for high-risk AML. We altered the language to ensure it was clear that those hospitalized for non-intensive chemotherapy are not eligible for study participation.

3) **Amendment 3 2/2018:** Minor adjustments to wording and grammar throughout the protocol. Added University of Pennsylvania as a study site (in addition to MGH and Duke).

4) **Amendment 4 3/2018:** temporary closure of University of Pennsylvania recruitment given that they had a chance in staffing for study research coordinator.

5) **Amendment 5 7/2018:** re-opening of the University of Pennsylvania after increase in staffing and hiring of a new research coordinator.

6) **Amendment 6 10/2018:** added Ohio State University as an additional site for the study

7) **Amendment 7 6/2019:** amended the protocol to incorporate a sub-protocol focused on conducting a secondary data analysis comparing patient-reported outcomes among patients receiving 7+3 versus Vyxeos (controlling for palliative care intervention)