SCOPE DCC Analytic Plan

Table of contents

1 Read Me First

This is a Quarto book for 2025 SCOPE DCC project.

A Visual Tool to Help Develop a Statistical Analysis Plan for Randomized Trials in Palliative Care

Collaboration with a statistician about the design of a statistical analysis plan can be enhanced by illustrating how statisticians conceptualize their task. This conceptualization can be represented by a directed acyclic graph (DAG), which illustrates the statistician's approach and also provides an actionable tool to assist in the development of the plan.

Collaboration with a statistician can be enhanced by understanding how they conceptualize questions of study design and data analysis. In the language of constructivism: by explicitly encountering their "mental maps" of these topics. One such mental map pertains to the development of a statistical analysis plan (SAP), an outline of which is one of each team's work products. Here, we use a figure to describe how statisticians typically conceptualize SAPs, and then illustrate how this figure can be used to develop an outline of a generic SAP for a randomized trial of a pain coping intervention in palliative care. It is our hope that making this conceptual framework explicit can help support more productive interactions between palliative care researchers and statisticians.

The main documents are stored in this link

Content

```
 [1] "00_activity_log.qmd"              "00_sap_revisions.qmd"
 [3] "00_template.qmd"                  "10_administrative_information.qmd"
 [5] "11_study_information.qmd"         "12_roles_and_responsibilities.qmd"
 [7] "13_sap_information.qmd"           "14_project_information.qmd"
 [9] "15_investigator_agreement.qmd"    "16_signatures.qmd"
[11] "20_study_overview.qmd"            "21_background.qmd"
[13] "22_aims_and_hypotheses.qmd"       "23_interested_variables.qmd"
[15] "24_causal_dag.qmd"                "25_inclusion_exclusion.qmd"
[17] "26_recruitment.qmd"               "27_site.qmd"
[19] "28_timeline.qmd"                  "29_stopping.qmd"
[21] "30_study_design.qmd"              "31_sample_size.qmd"
```

```
[23] "32_interim_analyses.qmd"           "33_data.qmd"
[25] "34_missing_data.qmd"               "35_subjects.qmd"
[27] "36_randomize.qmd"                  "37_fidelity.qmd"
[29] "38_measures.qmd"                   "39_provisions_safety.qmd"
[31] "40_statistical_analysis.qmd"       "41_descriptive_statistics.qmd"
[33] "42_analysis_methods.qmd"           "43_additional.qmd"
[35] "43_sensitivity_analysis.qmd"       "44_exploratory_analysis.qmd"
[37] "45_software.qmd"                   "46_others.qmd"
[39] "47_simulations.qmd"                "50_tables_shells.qmd"
[41] "51_a_tables.qmd"                   "51_b_tables.qmd"
[43] "52_figures.qmd"                    "53_examples.qmd"
[45] "60_additional_information.qmd"     "61_appendices.qmd"
[47] "62_glossary.qmd"                   "63_addenda.qmd"
[49] "70_references.qmd"                 "index.qmd"
```

Folders

Documents

```
[1] "analytic_plan_aim1.doc"
[2] "analytic_plan_aim2.doc"
[3] "analytic_plan_aim3.doc"
[4] "analytic_plan_aim4.doc"
[5] "analytic_plan_aim5.doc"
[6] "analytic_plan_template_20240925.doc"
[7] "klc_protocol_track_changes_20240226.doc"
[8] "project_timeline.xlsx"
[9] "samsa_colborn_2023.pdf"
```

Data

```
[1] "data-raw.R"
```

Codes

```
[1] "00_utils.R"      "01_plot_theme.R"
```

Figures and Tables

```
[1] "F22_table1_outcomes.png"  "F23_causal_dag1.png"
[3] "F23_causal_dag2.png"      "F28_table2_procedure.png"
[5] "F30_table3.png"           "F33_table6.png"
[7] "F37_table4_fidelity.png"  "F38_table5.png"
```

Reports

2 Activity Log

20250205

- ☒ General SCOPE DCC / Grant Document Review
- ☒ Read through the analytic plan for Link
- ☒ This is a clustered randomized trial
    - ☒ section 9.4 Analysis Section
    - ☒ section 11.2 Data Management page 7
    - ☒ write a statistical analysis plan for each analysis
    - ☒ primary - > caregiver
- ☒ Randy will map the protocol to the databases to the analysis
- ☒ What are the superior hypothesis and reject the H_0
- ☒ You are fine!

Notes: Yizhou is working on the truncated by death cases; probably can be shifted into the primary data analysis plan.

20250305

- ☒ Build up the analysis plan template and the package functions
- ☒ Reference the SAP paper
- ☒ Ask Katie for approval on the package project
- ☒ You are magnificent!

20250404

- ☒ Talking with EJC about the package project
- ☐ Filling up the project and add comments
- ☐ Build up the analysis plan for multiple members
- ☐ Check how to build up the website
- ☐ Check how to use github to include other people
- ☒ You are cat's meow!

20250408

- ☒ Filling up the project and add comments
- ☒ Writing functions to create qmd files
- ☒ New aim function and files
- ☐ Build up the analysis plan for multiple members
- ☐ Check how to build up the website
- ☐ Check how to use github to include other people
- ☒ You are excellent!

20250410

- ☐ how to use argument in the YML
- ☐ generate reports and analysis without coding
- ☐ working on the figure and table
- ☐ aim 1 analysis plan (to Katie)
- ☒ You are premium!

20250415

Goal for this meeting with Katie

- ☒ show the demo case of the template / package
- ☐ better organize the template
- ☐ add the function to create the qmd file or just copy paste
- ☐ subfolder or generate the files all in one
- ☐ styles and formatting?
- ☐ asking help for the website
- ☒ You are swell!

3 SAP revisions

3.0.1 SAP revision history with dates

3.0.2 Justification for each SAP revision

3.0.3 Timing of SAP revision

Timing of SAP revision in relation to any interim analyses or submissions

Part I

Administrative Information

Title

Specialty Compared to Oncology Delivered Palliative Care for Patients with Acute Myeloid Leukemia – SCOPE-Leukemia

Protocol Version

Version 1.9, 2025-04-08

Study Information and Background

?@sec-study_information

Responsibilities

Section 5.0.2 and #sec-statisticians

Project Information

?@sec-project_information

Agreements and Signatures

4 Study Information

Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle

Specialty Compared to Oncology Delivered Palliative Care for Patients with Acute Myeloid Leukemia – SCOPE-Leukemia

4.0.1 Subtitles

Listing out the subject subtitles probably with each aim with cross links.

4.0.2 Trial registration number

4.0.3 Protocol version number

Version 1.9

4.0.4 IRB number

4.0.5 Department

5 Responsibilities

5.0.1 Sponsor-Investigator

- Name: Areej El-Jawahri MD
  - Institution: Massachusetts General Hospital
  - E-mail Address: ael-jawahri@partners.org

5.0.2 Principal Investigators (PI)

- Name: Areej El-Jawahri MD
  - Institution: Massachusetts General Hospital
  - Address – 55 Yawkey Street, Yawkey 9E, Boston MA 02114
  - Telephone – 617-724-4000
  - Fax – 617-643-5843
  - E-mail Address: ael-jawahri@partners.org
- Name: Jennifer Temel MD
  - Institution: Massachusetts General Hospital
  - Address – 10 North Grove Street, Boston MA 02114
  - Telephone – 617-724-4000
  - Fax – 617-726-0543
  - E-mail Address: jtemel@mgh.harvard.edu

5.1 SAP Authors

5.1.1 Statisticians

- Name: Katie Colborn PhD
  - Institution: University of Colorado Denver - Anschutz Medical Campus
  - Telephone – 303-946-3578
  - Fax – 303-946-3578
  - E-mail Address: katie.colborn@cuanschutz.edu

- Name: Elizabeth Juarez-Colunga
  - Institution: University of Colorado Denver - Anschutz Medical Campus
  - Telephone – 303-724-6971
  - E-mail Address: elizabeth.juarez-colunga@cuanschutz.edu

5.1.2 Other Contributors

- Name: Randy Jin
  - Institution: University of Colorado Denver - Anschutz Medical Campus
  - Telephone – 314-305-1234
  - E-mail Address: xin.2.jin@cuanschutz.edu

6 Project Information

6.0.1 Project folder location

6.0.2 Project goals

- ☒ manuscript
- ☒ abstract
- ☒ presentation
- ☒ paper
- ☒ package and template
- ☒ poster

6.0.3 Project deadlines (of listed goals)

6.0.4 Effort estimate

7 Investigator Agreement

Confirmation that BERD Method Core's collaborative process has been reviewed:

- all statistical analyses included in an abstract or manuscript should reflect the SAP;
- no changes should be made to the SAP without discussing with the SAP authors;
- all biostatisticians on the SAP are co-authors on the manuscript
- publications resulting from the SAP must cite grant number UL1TR002553 and be submitted to PubMed Central

7.1 Extra Documents

8 Signatures

This is a signature block to include your name, title, and contact information in your signature block.

You can also include a logo or image.

8.0.1 Signatures of SAP author

8.0.2 Senior statistician

8.0.3 Principal investigator

Part II

Study Overview

This is a cluster randomized comparative effectiveness trial of primary palliative care (PC) versus specialty PC in 1150 patients with acute myeloid leukemia (AML) and their caregivers.

The primary objective is to determine whether primary PC is non-inferior to specialty PC for improving quality of life (QOL) in patients with AML. The primary hypothesis is that patients assigned to primary PC will report QOL that is non-inferior to patients receiving specialty PC, with a non-inferiority margin of 5.0 points. This study includes several secondary and exploratory endpoints as described in section **?@sec-endpoints**.

Study-Wide Number of Subjects

The study sample will include 1150 patients with AML and up to 1150 caregivers. Patients can participate in the study without a caregiver, and we estimate that approximately 50% of patients will have a caregiver participate in the study. Thus, we anticipate the caregiver sample will be approximately 575 participants.

9 Background

9.0.1 Patients with AML have a sudden life-threatening illness requiring urgent therapy

AML is an aggressive disease, characterized by an abrupt onset, an urgent need to initiate treatment, and a poor prognosis with 80% risk of death at five years (Alibhai et al. 2007, 2015; Burnett et al. 2010; Walter and Estey 2020; Vey 2020). Most patients with AML are treated with chemotherapy drugs that require hospitalization due to significant toxicities and potentially life-threatening complications, such as bleeding and sepsis (Rodin et al. 2013; Zimmermann et al. 2013; Zittoun, Achard, and Ruszniewski 1999; A. R. El-Jawahri et al. 2015a). Patients with AML often present to medical attention without prodromal symptoms, so they are quite shocked to learn that they have a life-threatening illness and must be immediately hospitalized to receive intensive chemotherapy (Alibhai et al. 2007, 2015; Burnett et al. 2010).

9.0.2 Patients with AML face substantial physical and psychological symptoms

During their hospitalization for chemotherapy, patients with AML often experience difficult physical symptoms, including fevers, fatigue, pain, insomnia, mucositis, nausea, vomiting, and diarrhea that negatively impact their quality of life (QOL) and physical function (Rodin et al. 2013; Zimmermann et al. 2013; Zittoun, Achard, and Ruszniewski 1999; A. R. El-Jawahri et al. 2015a; A. El-Jawahri et al. 2019; Loh et al. 2019; Wiese and Daver 2018). Psychological symptoms are also quite prominent in these patients, with over one-third experiencing acute stress reactions from the shock of their diagnosis and need for urgent hospitalization (Rodin et al. 2013; Zimmermann et al. 2013; Zittoun, Achard, and Ruszniewski 1999; A. R. El-Jawahri et al. 2015a; A. El-Jawahri et al. 2019; Loh et al. 2019; Wiese and Daver 2018; Nissim et al. 2013, 2014; Papadopoulou, Johnston, and Themessl-Huber 2013; Farsi, Nayeri, and Negarandeh 2012; Gheihman et al. 2015; V. Ghodraty-Jabloo et al. 2015; Vida Ghodraty-Jabloo et al. 2015). Notably, the psychological burden during this hospitalization also impacts patients' long-term QOL, mood, and adaptation to their illness (V. Ghodraty-Jabloo et al. 2015; Vida Ghodraty-Jabloo et al. 2015). Up to 40% of patients with AML suffer from post-traumatic stress symptoms due to the trauma of their diagnosis (Smith et al. 1999; Jacobsen et al. 1998, 2002; Mundy et al. 2000).Therefore, addressing the physical and psychological needs of hospitalized patients with AML has the potential to improve their outcomes significantly both during their hospitalization and in the long-term.

9.0.3 Patients with AML face difficult decisions about treatment

Many treatments are available that offer a chance of cure for patients with AML, including stem cell transplant. However, the chance of cure is small and most patients with AML unfortunately die of their illness (Schlenk et al. 2017; Ganzel et al. 2018). Consequently, to make informed decisions about whether to receive additional treatment, patients with AML must understand their prognosis and likelihood of cure (A. El-Jawahri et al. 2020, 2018). Unfortunately, data suggest that 90% of patients with AML report overly optimistic estimates of their prognosis (A. El-Jawahri et al. 2018). Thus, they are unprepared to make difficult decisions that require them to balance the risks and benefits of treatments that offer an uncertain chance of cure, but will worsen their QOL and require them to spend additional time in the hospital (A. R. El-Jawahri et al. 2015a). Therefore, patients with AML face considerable uncertainty and often misunderstand their prognosis, limiting their ability to make informed decisions about treatment.

9.0.4 Patients with AML rarely discuss their end-of-life (EOL) care preferences

Due to the chance of cure even after multiple therapies, oncology clinicians often defer engaging in conversations with patients with AML about their EOL care preferences (A. El-Jawahri et al. 2020). As the majority of these patients die, it is imperative that oncology clinicians elicit their goals and help them make decisions about their EOL care. Unfortunately, studies show that patients with AML do not engage in timely discussions with their clinicians about their care preferences and consequently receive aggressive care at the EOL (V. Ghodraty-Jabloo et al. 2015; A. R. El-Jawahri et al. 2015b; T. W. LeBlanc and Erba 2019; T. W. LeBlanc, Egan, and Olszewski 2018; D. Hui et al. 2014; A. A. El-Jawahri et al. 2015; A. El-Jawahri et al. 2020; Bosshard et al. 2018; Klepin, Rao, and Pardee 2014). Specifically, while many patients with cancer express a preference to die at home and minimize time in the hospital, 80% of patients with AML are hospitalized in the last month of life, with 50% dying in the hospital. Over half receive chemotherapy in the last month of life and 30% die in the intensive care unit (ICU) (V. Ghodraty-Jabloo et al. 2015; A. R. El-Jawahri et al. 2015b; T. W. LeBlanc and Erba 2019; T. W. LeBlanc, Egan, and Olszewski 2018; D. Hui et al. 2014; A. A. El-Jawahri et al. 2015; A. El-Jawahri et al. 2020; Bosshard et al. 2018; Klepin, Rao, and Pardee 2014). Evidence-based interventions are needed to enhance patient–clinician communication and optimize EOL care for patients with AML.

9.0.5 Caregivers of patients with AML experience tremendous burden and distress

The family and close friends ("caregivers") of patients with AML play a critical role in their care, but also experience distress as they face the shock of the patient's diagnosis and cope with uncertainty (A. El-Jawahri et al. 2019; Jia et al. 2015; Gemmill et al. 2011; Fife et al.

2009). During the patient's hospitalization for treatment, caregivers report a marked decline in their QOL and mood as they witness the patient struggle with side effects (A. El-Jawahri et al. 2019). After the patient is discharged from the hospital, the caregiver helps manage the patient's symptoms, attends multiple oncology appointments, coordinates medical care, and prepares for subsequent hospitalizations (Grover et al. 2019). Caregivers experience the highest burden and psychological distress when caring for patients with AML near the EOL (Grover et al. 2019; Gerlach, Alt-Epping, and Oechsle 2019). Not surprisingly, caregivers of patients with AML have disruptions in their professional and personal lives. Thus, caregivers of patients with AML would benefit from support as they navigate the patient's illness.

9.0.6 Specialty palliative care improves outcomes for patients and their caregivers

A growing body of evidence has demonstrated the essential role of specialty palliative care (PC) clinicians in the care of patients with advanced solid tumors (J. S. Temel et al. 2010, 2017; M. Bakitas et al. 2009; M. A. Bakitas et al. 2015; Zimmermann et al. 2014). Integrating PC with oncology care from the time of diagnosis for patients with advanced solid tumors improves patients' QOL, psychological health, and EOL care (J. S. Temel et al. 2010, 2017; M. Bakitas et al. 2009; M. A. Bakitas et al. 2015; Zimmermann et al. 2014). Emerging data have similarly shown the benefits of specialty PC for patients with hematologic malignancies (Areej R. El-Jawahri et al. 2016, 2017; Areej El-Jawahri et al. 2021). We recently completed a multi-site randomized trial of specialty PC versus usual care in hospitalized patients with AML (Areej El-Jawahri et al. 2021). Patients assigned to specialty PC met with a PC clinician at least twice weekly during their hospitalization for chemotherapy and subsequent hospitalizations up to one year. Specialty PC improved patients' QOL, depression and anxiety symptoms, as well as post-traumatic stress symptoms (Areej El-Jawahri et al. 2021). Importantly, specialty PC led to clinically meaningful and sustained improvements in patients' QOL and psychological distress for six months after initiating chemotherapy (Areej El-Jawahri et al. 2021). Patients receiving specialty PC were also more likely to discuss their EOL care preferences and less likely to receive chemotherapy in the last month of life (Areej El-Jawahri et al. 2021). Thus, involvement of specialty PC improves the experience and outcomes of patients with serious cancer and their caregivers.

9.0.7 Specialty PC is not an accessible or scalable care model

Despite the benefits of specialty PC for patients with cancer, it is not feasible to provide this care for all patients given the limited availability of trained PC clinicians (David Hui et al. 2010; Lupu, Hospice, and Force 2010; Blackhall et al. 2016). Nearly half of National Cancer Institute-designated cancer centers do not have the specialty PC workforce to provide care for their patients with cancer (David Hui et al. 2010; Lupu, Hospice, and Force 2010; Blackhall et al. 2016). Due to these workforce shortages, most specialty PC is triaged to provide care for patients with incurable cancer at the EOL. Thus, despite the growing evidence base,

substantial challenges limit the scalability and dissemination of this care model, especially in caring for patients with hematologic malignancies (A. El-Jawahri et al. 2020; Thomas W. LeBlanc and El-Jawahri 2015). Moreover, oncology clinicians caring for patients with hematologic malignancies rarely consult specialty PC as they view providing PC within their scope of practice (A. El-Jawahri et al. 2020; Thomas W. LeBlanc and El-Jawahri 2018; Areej El-Jawahri et al. 2018; David Hui et al. 2015). Furthermore, given the complex chemotherapy regimens used to treat patients with AML and their side effects, oncology clinicians may be the ideal clinicians to address these needs (A. El-Jawahri et al. 2020; Thomas W. LeBlanc and El-Jawahri 2018; Areej El-Jawahri et al. 2018; David Hui et al. 2015).

9.0.8 Primary PC may be an alternative care model to specialty PC

Training oncology clinicians to incorporate PC skills into their care practice (i.e., "primary PC") is an alternative strategy to having specialty trained PC clinicians care for all patients with cancer. Recent studies have shown that primary PC interventions in which oncology clinicians are trained to address patient's symptoms and engage in serious illness conversations are feasible, acceptable, and improve patient outcomes (Bernacki et al. 2019; Paladino et al. 2019). These interventions have been shown to increase oncology clinicians' knowledge about symptom assessment and management, as well as their comfort managing psychological distress (Epstein et al. 2017; Reddy et al. 2019; Schenker et al. 2015). In a cluster randomized trial in which oncology clinicians were trained in serious illness communication, patients receiving primary PC were more likely to have documented EOL discussions and reported lower anxiety and depression symptoms (Bernacki et al. 2019; Paladino et al. 2019). While these primary PC studies are promising, it remains unknown how primary PC compares with specialty PC for improving QOL and EOL care for patients with cancer (A. El-Jawahri et al. 2020; Kavalieratos et al. 2016). Recent systematic reviews highlight the need for comparative effectiveness trials of primary versus specialty PC, to determine how to best meet the needs of patients with serious cancers, and especially those with hematologic malignancies (A. El-Jawahri et al. 2020; Kavalieratos et al. 2016).

9.1 Resources Available

9.1.1 Team Qualifications and Oversight

Due to the size and scope of this award, we have chosen a leadership plan with dual study PIs (Drs. Areej El-Jawahri and Jennifer Temel). The dual PIs have a long-standing history of collaboration with over 20 funded research projects, and led the specialty PC trial in leukemia, which serves as the preliminary data for the current project. The dual PIs pre-existing relationship, including a history of successful collaborations on grant applications and manuscripts in high tier medical journals, and complimentary experience conducing PC trials, will ensure

they provide effective leadership of this study. The University of Colorado Data, Informatics, and Statistics Core will serve as the DCC. Dr. Colborn will provide independent leadership of the DCC and have autonomy over data integrity, data quality, and data analysis during both the study phases.. Prior studies have highlighted the unique challenges of conducting PC research trials with adequate methodological oversight and appropriate data analytical approach. Specifically, given their experience with PC research methodology, our DCC possess the necessary expertise to: - 1) ensure adequate oversight of data collection procedures for participant-reported outcomes - 2) address challenges of attrition and missing data due to death in PC research - 3) implement statistical methods to address missing data - 4) measure PC intervention fidelity. Furthermore, the DCC investigative team has substantial expertise in serving as the DCC for multiple large-scale multi-site projects.

9.1.2 Other Resources

We solicited participating sites through The Palliative Care Research Cooperative (PCRC) with medium to large leukemia practices to ensure that each site would see a minimum of 50 new patients with AML per year. We also chose sites that have an inpatient specialty PC practice to accommodate patients who are randomized to receiving specialty PC. Prior to submitting this project, we conducted interviews with 35 sites and chose 20 sites with appropriate infrastructure to conduct the study. As many of these sites are tertiary care centers, we estimate that 15% of new patients will be second-opinion consultations only and therefore ineligible. We estimate that each site will have a minimum of 40 eligible patients per year. At MGH, we have enrolled 70% of eligible patients with AML in our prior PC trials. Since the proposed study is a cluster randomized trial, we anticipate that enrollment rates will be higher than prior studies, as patients are not being randomized. Nonetheless, we conservatively estimate that at least 60% of eligible patients will enroll in the study. In our prior studies, 60% of patients who enrolled had a caregiver who was willing to participate, so we conservatively estimate caregiver enrollment rates of approximately 50%. Therefore, we are confident in our ability to achieve our proposed enrollment goals for patients and caregivers.

10 Preliminary Data

List of all outcome/endpoint variables, with a description of their coding/units, timing, and source, corresponding to the statistical hypotheses. If any variables are defined using ICD or CPT codes, list them out.

10.0.1 Burden of AML

We demonstrated that patients with AML have a marked decline in their quality of life (QOL) during chemotherapy [B = -9.5, P < 0.001] and that the proportion with clinically significant depression increases during the first month after treatment (34% to 46%, P = 0.01)(A. El-Jawahri et al. 2019). Caregivers similarly experience a deterioration in their QOL and the proportion with clinically significant depression almost doubles in the first month after treatment (17% to 31%, P = 0.03)(A. El-Jawahri et al. 2019). We have also shown that patients with AML spend two-thirds of their life from diagnosis to death in the hospital or clinic, and in the last month of life almost 90% are hospitalized, half receive chemotherapy, and one-third are admitted to the ICU (A. R. El-Jawahri et al. 2015a).

10.0.2 Specialty PC

The MGH research team has conducted six multi-site specialty PC trials in patients with cancer. In their landmark *New England Journal of Medicine* study, they showed that patients with advanced lung cancer assigned to specialty PC from the time of diagnosis had better QOL, less depression, higher rates of documented end-of-life (EOL) care preferences, lower rates of chemotherapy administration in the last month of life, and increased hospice utilization compared to patients receiving usual care (J. S. Temel et al. 2010). These findings were confirmed in a subsequent large-scale trial in patients with advanced lung and gastrointestinal cancers (Jerome S. Temel et al. 2016). Based on this work, specialty PC has become standard of care for patients with advanced solid tumors (Ferrell et al. 2016).

Recognizing that specialty PC was rarely involved in the care of patients with hematologic malignancies, we studied the first specialty PC intervention for patients with hematologic malignancies undergoing stem cell transplantation. This trial demonstrated that specialty PC improved key patient outcomes—including QOL, depression, and anxiety (**tab-outcomes?**; Areej R. El-Jawahri et al. 2016, 2017)—and caregiver depression and coping (Areej R. El-Jawahri et al. 2016, 2017). These benefits were sustained at 12- and 24-weeks post-transplant

with improvements in patient depression and post-traumatic stress symptoms (Areej R. El-Jawahri et al. 2016, 2017). Building on this work, we recently completed a multi-site randomized trial evaluating the efficacy of specialty PC for patients with AML. This study demonstrated early and sustained improvement in patients' QOL, depression, anxiety, and post-traumatic stress symptoms (**tab-outcomes?**; Areej El-Jawahri et al. 2021). Patients receiving specialty PC were also significantly more likely to discuss their EOL care preferences with their clinicians and less likely to receive chemotherapy in the last 30 days of life (Areej El-Jawahri et al. 2021). Thus, the MGH team has substantial experience conducting large-scale PC trials in oncology that will ensure the success of this project.

10.0.3 Primary PC

Our investigative team also has experience training clinicians to deliver primary PC. Dr. Yael Schenker conducted a single-arm pilot trial assessing the feasibility, acceptability, and perceived effectiveness of primary PC for patients with advanced cancer (Schenker et al. 2015). The primary PC intervention entailed training oncology clinicians to address symptoms, engage patients and caregivers in EOL discussions, provide emotional support, and coordinate care, especially at the EOL. All eligible oncology clinicians attended the training and felt it improved the quality of care they provided for patients with advanced cancer. Patients and caregivers reported high satisfaction with primary PC and perceived it as helpful in addressing symptoms, coping, and planning for the future (Schenker et al. 2015). Additionally, Dr. Vicki Jackson has expertise conducting primary PC training for clinicians in oncology and other medical specialties through her leadership of the Harvard Palliative Care Education and Practice course. More than 1200 clinicians have attended this course on the management of physical and psychological symptoms, coping, illness understanding, and EOL communication. Thus, our research team has the necessary expertise to train oncology clinicians successfully to deliver PC and evaluate the effectiveness of primary PC for patients with cancer.

10.0.4 Table Patient Outcomes with Specialty PC

```
knitr::include_graphics("figures/F22_table1_outcomes.png",
                        dpi = 30,)
```

Table 1: Patient Outcomes with S
Clinical Trial
Specialty PC in Stem Cell Transp
QOL at 2 weeks
Anxiety at 2 weeks
Depression at 2 weeks
QOL at 12 weeks
Depression at 12 weeks
PTSD at 12 weeks
Specialty PC in AML
QOL at 2 weeks
Anxiety at 2 weeks
Depression at 2 weeks
QOL at 12 weeks
Depression at 12 weeks
Anxiety at 12 weeks
PTSD at 12 weeks

Click to expand Table 1

Table 1: Patient Outcomes with Specialty PC

Clinical Trial	Intervention Effect (B)	95% CI	P-value
Specialty PC in Stem Cell Transplant			
QOL at 2 weeks	7.73	1.27, 14.19	0.019
Anxiety at 2 weeks	-2.25	-3.22, -1.29	<0.001
Depression at 2 weeks	-1.74	-3.01, -0.47	0.007
QOL at 12 weeks	5.34	0.04, 10.64	0.048
Depression at 12 weeks	-1.70	-2.75, -0.65	0.002
PTSD at 12 weeks	-4.34	-7.12, -1.57	0.002
Specialty PC in AML			
QOL at 2 weeks	8.85	0.43, 17.28	0.039
Anxiety at 2 weeks	-1.41	-2.56, -0.25	0.017
Depression at 2 weeks	-1.51	-2.80, -0.23	0.021
QOL at 12 weeks	11.11	3.15, 19.06	0.007
Depression at 12 weeks	-2.22	-3.59, -0.85	0.002
Anxiety at 12 weeks	-1.59	-2.85, -0.33	0.013
PTSD at 12 weeks	-3.91	-6.67, -1.16	0.006

```
\begin{table}[htbp]
  \centering
  \caption{Table 1: Patient Outcomes with Specialty PC}
  \begin{tabular}{@{} l c c c @{}}
    \toprule
    \textbf{Clinical Trial} & \textbf{Intervention Effect (B)} & \textbf{95\% CI} & \textb
    \midrule
    \textbf{Specialty PC in Stem Cell Transplant} &  &  &  \\
    QOL at 2 weeks & 7.73 & 1.27, 14.19 & 0.019 \\
    Anxiety at 2 weeks & -2.25 & -3.22, -1.29 & $<$0.001 \\
    Depression at 2 weeks & -1.74 & -3.01, -0.47 & 0.007 \\
    QOL at 12 weeks & 5.34 & 0.04, 10.64 & 0.048 \\
    Depression at 12 weeks & -1.70 & -2.75, -0.65 & 0.002 \\
    PTSD at 12 weeks & -4.34 & -7.12, -1.57 & 0.002 \\
    \addlinespace
    \textbf{Specialty PC in AML} &  &  &  \\
    QOL at 2 weeks & 8.85 & 0.43, 17.28 & 0.039 \\
    Anxiety at 2 weeks & -1.41 & -2.56, -0.25 & 0.017 \\
```

```
    Depression at 2 weeks & -1.51 & -2.80, -0.23 & 0.021 \\
    QOL at 12 weeks & 11.11 & 3.15, 19.06 & 0.007 \\
    Depression at 12 weeks & -2.22 & -3.59, -0.85 & 0.002 \\
    Anxiety at 12 weeks & -1.59 & -2.85, -0.33 & 0.013 \\
    PTSD at 12 weeks & -3.91 & -6.67, -1.16 & 0.006 \\
    \bottomrule
  \end{tabular}
\end{table}
```

10.1 Exposure variables

List of all exposure variables, with a description of their coding/units, timing, and source, corresponding to the statistical hypotheses. If any variables are defined using ICD or CPT codes, list them out.

10.2 Additional variables

List of any additional variables of interest (e.g. covariates, potential confounders, effect modifiers, etc.) in the analysis.

10.3 Data dictionary

Location of data dictionary (or provided as an appendix)

You can also use the `help()` function in R to get the information about the dataset `help(dataset)`.

10.4 Data transformations

Report category boundaries if continuous variables are collapsed into categories, and describe any other relevant data transformations

11 Inclusion Exclusion

The clinical research coordinator (CRC) at participating sites will identify all patients admitted to the hospital with a diagnosis of AML on a daily basis to identify potentially eligible patients. The patient eligibility criteria is similar to our prior specialty PC studies in this patient population.

11.1 Eligibility Criteria

11.1.1 Patient Eligibility Criteria

Patient Inclusion Criteria:

- Hospitalized patients (age > 18 years) with high-risk AML defined **as one of the following**:
  - 1) Patients with new diagnosis > 60 years of age
  - 2) An antecedent hematologic disorder
  - 3) Therapy related-disease
  - 4) Relapsed or primary refractory AML
- Receiving treatment with either:
  - a) intensive chemotherapy (7+3) or modification of this regimen on a clinical trial, or a similar intensive regimen requiring prolonged hospitalization;
  - b) hypomethylating agents +/- additional agents or modification of this regimen on a clinical trial

Patient Exclusion Criteria:

- 1) Patients with a diagnosis of acute promyelocytic leukemia
- 2) Patients with AML receiving supportive care alone
- 3) Patients with psychiatric or cognitive conditions which the treating clinicians believes prohibits informed consent or compliance with study procedures
- 4) Patients seen by a palliative care clinician [MD, DO, or APP] during two previous hospitalizations in the six months prior to enrollment

11.1.2 Caregiver Eligibility Criteria

Caregiver Inclusion Criteria:

- 1) Adult (> 18 years) relative or 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 them at least twice per week

11.1.3 Special Populations

We will not enroll the following special populations:

- adults unable to consent
- individuals who are not yet adults
- pregnant women
- prisoners.

12 Recruitment Methods

12.0.1 Study-Wide Number of Subjects

The study sample will include 1150 patients with AML and up to 1150 caregivers. Patients can participate in the study without a caregiver, and we estimate that approximately 50% of patients will have a caregiver participate in the study. Thus, we anticipate the caregiver sample will be approximately 575 participants. Repeated information

12.0.2 Study-Wide Recruitment Methods

Prior to the study start, the site investigators will meet with the leukemia clinicians to review recruitment and enrollment procedures.

The CRC will communicate with the leukemia clinicians (the physicians and advanced practice providers who care for the patient in the outpatient setting or during their hospitalization) via email, electronic communication through the health record, or verbally to notify them that the patient is eligible for the study and inquire about concerns regarding their participation. If the clinicians have objections to the patient participation in the study, the CRC will document the reason and not approach those individuals. If the leukemia clinicians have no objections, the CRC will approach patients for study participation within three business days of initiating therapy and inform them that their clinicians have agreed for them to be contacted for the study and review the consent document which details the nature of all study procedures. We have separate consent forms for sites randomized to specialty PC or primary PC. The CRC will obtain written informed consent from the patient and provide them with a copy of the signed consent form.

Study participants will complete baseline self-report assessments at the time of providing informed consent for the study. If a patient signs the consent form but does not complete the baseline assessment within two business days, they will not be registered on the study and will not count towards accrual numbers. To ensure adequate sample size, we will enroll additional participants for any participants who withdraw, or transfer care within the first 30 days of enrollment. We will increase the total accrual goal within each cluster to account for patients who withdraw, or transfer care within 30 days of the study period.

Patients who agree to participate in the study will 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 three business days after the patient provides written informed consent. We have separate consent forms for caregivers at sites randomized to specialty PC or primary PC. Caregivers can enroll in the study in-person with a written informed consent or over the telephone with a verbal consent. Caregivers will complete baseline self-report assessments (in-person, over telephone, or via email) on the same day as providing informed consent or within a one-week window. If a caregiver provides consent but does not complete the baseline assessment, they will not be included as study participants.

Patients and caregivers who speak other languages 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. Patients who speak other languages will be given the full consent form in their respective language for signing. The consent form will be signed by the participant, and by a witness. The witness will be either an interpreter or a family member. Potentially eligible caregivers will either provide written informed consent or over the telephone with a verbal consent with the assistance of an interpreter (or family member if interpreter is unavailable).

We will also recruit key informants for the qualitative portion of this study. Specifically, we will conduct qualitative interviews stratified by the size of the leukemia program at participating sites. For each key informant group, we will interview 30 individuals, consisting of 10 from each size stratum (small, medium, or large leukemia program). Specifically, we will conduct interviews with:

- 1) patients with AML receiving specialty PC and caregivers;
- 2) patients with AML receiving primary PC and caregivers;
- 3) oncology clinicians;
- 4) PC clinicians;
- 5) hospital leaders to identify facilitators and barriers to the adoption, implementation, and maintenance of primary PC and specialty PC.

Key informants will provide written or verbal consent over the telephone (given the COVID-19 pandemic).

All study participants (patients, caregivers, and key informants) will be provided a copy of their respective consent forms.

We are requesting a Waiver of Written Documentation of Consent This Waiver is being requested to assist with caregiver and key informant 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 caregivers and key informants and is necessary for our research procedures to continue.

We are requesting a HIPAA Waiver of Authorization to Review Preparatory to Research from the IRB. We are requesting this Waiver to identify potential patient 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 - (3) the Protected Health Information for which we are requesting access is necessary for the research purposes

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101.

For registration of patients from DF/HCC institutions, study staff will complete the 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. MGH study staff may also call the study staff at the participating site to verbally confirm registration.

12.1 Prior Approvals

The DF/HCC will serve as the single IRB of record for this trial. We will ensure that all participating sites have a reliance agreement to the DF/HCC IRB.

12.2 Recruitment Methods

Please see above for recruitment methods across all study sites. The research staff may provide potentially eligible patients with an informational sheet about the study (Appendix A, Appendix B). Participants will not receive payments for their participation in the study.

12.3 Consent Process

The CRC will obtain written informed consent for patients participating in the study in a private hospital room. Participants will have up to three business days from the initiating of therapy for AML to consent for the study. The CRC will review the consent from with

potential participants, which will clearly detail the nature of the study procedures, the time requirements, and the frequency of self-reported assessments. We will have separate consent forms for sites that are randomized to specialty PC or primary PC. The CRC will obtain written informed consent from the participant and provide them with a copy of the signed consent form.

Patients who agree to participate in the study 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 three business days after the patient provides written informed consent. We will have a separate consent form for caregivers at sites randomized to specialty PC or primary PC, 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. Patients and/or caregivers who refuse study participation will be asked the reason for deferring. Caregivers will complete baseline self-report assessments on the same day as providing informed consent or within a one-week window. If caregivers provide consent, but do not complete baseline questionnaire, they will not count towards the caregiver accrual numbers.

Patients and caregivers who speak other languages 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. Patients who speak other languages will be given the full consent form in their respective language for signing. The consent form will be signed by the participant, and by a witness. The witness will be either an interpreter or a family member. Potentially eligible caregivers will either provide written informed consent or over the telephone with a verbal consent with the assistance of an interpreter (or family member if interpreter is unavailable).

We will also consent key informants for the qualitative portion of this study. Specifically, we will conduct qualitative interviews stratified by the size of the leukemia program at participating sites. For each key informant group, we will interview 30 individuals, consisting of 10 from each size stratum (small, medium, or large leukemia program). Specifically, we will conduct interviews with 1) patients with AML receiving specialty PC and caregivers; 2) patients with AML receiving primary PC and caregivers; 3) oncology clinicians; 4) PC clinicians; and 5) hospital leaders to identify facilitators and barriers to the adoption, implementation, and maintenance of primary PC and specialty PC. Key informants will provide written or verbal consent over the telephone (given COVID-19 pandemic).

12.4 Process to Document Consent in Writing

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

All patients participating in the study will provide written informed consent. Caregivers and key informants 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

12.5 Drugs or Devices

Not applicable

13 Multi-Site Research

13.0.1 Clinical Coordinating Center (CCC)

MGH will serve as the Clinical Coordinating Center (CCC) for this trial. The CCC will:

- 1) conduct trainings for site PIs and CRCs to ensure consistent recruitment and enrollment procedures across sites, for PC clinicians for sites randomized to specialty PC, and oncology clinicians for sites randomized to primary PC;
- 2) ensure regulatory compliance across sites by obtaining single IRB reliance agreements;
- 3) perform site visits to monitor study progress and ensure compliance with study procedures;
- 4) conduct monthly meetings with the site PIs and CRCs to address any study issues and challenges;
- 5) review data collection reports generated by the Data Coordinating Center (DCC) and provide feedback to the site PIs to ensure high-data quality;
- 6) review intervention fidelity reports generated by the DCC and provide feedback to individual clinicians at participating sites to ensure adherence to intervention delivery.

13.0.2 Study Staff Training

We will conduct an in-person training (or over video given COVID-19 pandemic) at MGH for the site PIs and the CRCs to ensure consistent enrollment procedures across sites. We will train the investigative team in how to:

- 1) identify potentially eligible patients;
- 2) communicate with leukemia clinicians about patient eligibility;
- 3) obtain informed consent from patients and caregivers;
- 4) ensure intervention delivery and data collection.

13.0.3 Data Coordinating Center (DCC) Functions

Data and Statistics Organization and Function: The DCC will lead the design and implementation of the statistics, informatics, and data management systems for the study. As part of the University of Colorado Data Informatics and Statistics Core, the DCC will work with the MGH investigative team to develop, implement, and maintain systems for a central data repository. The DCC has substantial expertise in statistical design and analysis, and creation of a standardized data element (SDE) dictionary with a case report form (CRF) library. The DCC will act independently in its management and analysis of data; however, the development of the data collection systems will be done in collaboration with the MGH investigative team.

All data collected at participating sites will remain confidential and will be collected via 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. All protected health information will be labeled as such in REDCap with only site personnel having access to protected health information at their respective sites. The MGH study team and the DCC will also have access to protected health information at all study sites via REDCap to conduct data monitoring queries and ensure data fidelity.

13.0.4 Setting

Participants will be recruited for study participation across 20 sitesPatients will be approached for study participation in their private hospital room during their hospitalization for AML. Caregivers will be approached for study participation in-person in a private hospital room or over the telephone. For completion of follow-up assessments, participants can be approached on the inpatient unit in a private room, during a clinic visit in a private space, or over the telephone.

14 Timeline

Patients and their caregivers will remain on study until the patient's death or up to 5 years after enrollment. The funding agency requires that we conduct this study in two phases, designated phase 1 and phase 2. Phase 1 will be conducted during the first 18 months and phase 2 will be conducted during the final five years of the 78-month study period.

During phase 1, we will complete study training, institute the study protocol, and enroll approximately 40 patients and 20 caregivers at four of the 20 participating sites. The four sites participating in phase 1 will be randomized in 1:1 fashion to specialty PC versus primary PC without any stratification. At the end of the 18-month study period, we will conduct study training and institute the study protocol at the other 16 sites. During phase 2, the 16 sites will be randomized to specialty PC versus primary PC stratified by percent minority population to ensure a balanced proportion of minority participants across the arms. During the remainder of the study period, we will enroll additional patients to achieve our study enrollment goal of 1150 patients. Table 2 (**tab-table2?**) depicts the study timeline and procedures:

14.0.1 Table2: Study Procedures

```
knitr::include_graphics("figures/F28_table2_procedure.png",
                        dpi = 10)
```

Initiate Phase 1 (Months 0-6)	• Select four • Randomize • Complete t
Conduct Phase 1 Initiate Phase 2 (Months 6-18)	• Enroll appr • Collect part • Complete t • Randomize
Conduct Phase 2 (Months 18-66)	• Enroll addi across al • Conduct sp • Collect part • Conduct qu
Complete Study Procedures (Months 66-78)	• Complete d • Conduct an • Complete d

Click to expand Table 2

Table 2: Study Procedures	
Initiate Phase 1 (Months 0-6)	- Select four sites (two from each group) to participate in phase 1 - Randomize sites participating in phase 1 - Complete training for phase 1 sites
Conduct Phase 1 / Initiate Phase 2 (Months 6-18)	- Enroll approximately 40 patients and up to 20 caregivers at four phase 1 sites -Collect participant-reported data from participants in phase 1 - Complete training for sites that did not participate in phase 2 - Randomize sites participating in phase 2
Conduct Phase 2 (Months 18-66)	- Enroll additional patients to reach sample of 1150 patients and up to 1150 caregivers across all sites - Conduct specialty PC and primary PC refresher training on an annual basis - Collect participant-reported and chart review data on all study participants - Conduct qualitative interviews with key informants
Complete Study Procedures (Months 66-78)	- Complete data collection with a minimum of 1-year follow-up on all study participants - Conduct and analyze qualitative interviews with key informants - Complete data analyses

15 Study Endpoints

15.1 Primary Endpoint

- To establish that primary PC is non-inferior to specialty PC in patient-reported QOL over at 12 weeks

15.2 Secondary Endpoints

- To assess whether primary PC is non-inferior to specialty PC with respect to patient-reported QOL at 1week-2 and longitudinally2 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to depressions symptoms at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to anxiety symptoms at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to post-traumatic stress (PTSD) symptoms at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to patient-reported EOL communication at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to chemotherapy administration in the last 30 days of life
- To assess whether primary PC is non-inferior to specialty PC with respect to caregiver QOL at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to caregiving burden at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to caregiver depression symptoms at 12 weeks
- To assess whether primary PC is non-inferior to specialty PC with respect to caregiver anxiety symptoms at 12 weeks

15.3 Exploratory Endpoints

- To compare the rate of change in patient-reported QOL longitudinally over 24 weeks between those receiving primary PC versus specialty PC

- To compare patient prognostic understanding between those receiving primary PC versus specialty PC.
- To compare patient coping between those receiving primary PC versus specialty PC
- To compare hospitalization in the last 30 days of life between those receiving primary PC versus specialty PC
- To compare intensive care unit admissions in the last 30 days of life between those receiving primary PC versus specialty PC
- To compare hospice utilization between those receiving primary PC versus specialty PC
- To explore differences in hospice length-of-stay between those receiving primary PC versus specialty PC
- To compare patient symptom burden between those receiving primary PC versus specialty PC.
- To compare patients' perception of patient-centeredness of care (i.e., acceptability and satisfaction) between those receiving primary PC versus specialty PC
- To compare caregiver-reported EOL communication between those receiving primary PC versus specialty PC
- To compare caregiver prognostic understanding between those receiving primary PC versus specialty PC
- To compare caregiver coping between those receiving primary PC versus specialty PC

16 Aims and Hypotheses

List of all scientific aims/objectives of the study, with specifications of primary, secondary, etc.

List of all statistical hypotheses (corresponding to the scientific aims), with specifications of primary, secondary,

16.0.1 Aim 1

To determine whether primary PC is non-inferior to specialty PC for improving QOL in patients with AML: We will begin with descriptive and graphical summaries of the endpoints to evaluate whether regression modeling assumptions are met and/or whether there are outliers that might be data entry errors. We will use an intention-to-treat approach for treatment group comparisons and report results using the CONSORT extension to cluster randomized trials. We chose an intention-to-treat approach for the primary analysis in our study as it 1) preserves the advantage of randomization and 2) we anticipate minimal cross-contamination in this cluster randomized clinical trial between study groups, which further enhances the fidelity of an intention-to-treat analysis. Nonetheless, we will closely track the extent of contamination in both study groups. We will also assess for potential factors that are associated with non-adherence to the assigned PC model such as age, sex, race/ethnicity, time from diagnosis, underlying leukemia diagnosis, leukemia risk, and institutional factors that might be associated with non-adherence (leukemia volume, size of leukemia program, and other institutional supportive care initiatives). We will also conduct and report per protocol analyses using inverse probability weighting (IPW) to provide robust statistical estimates for the primary and secondary outcomes in this trial. As the goal of the proposed study is to establish that patient-reported QOL with primary PC is non-inferior to specialty PC, all statistical tests for non-inferiority will be one-sided with an alpha level of 0.025. The primary endpoint of the study is to compare patient QOL (FACT-Leukemia) scores at week 12 between the study groups using linear mixed (LMM) effect models of longitudinal data with QOL estimated at each time point, with random effects for cluster and subject. The use of mixed models will allow us to account for dependency among longitudinal outcomes within a cluster and within an individual and to control for demographic and clinical factors (as necessary for any imbalances in baseline variables). Each time point will be included as a fixed factor with baseline as the reference group. Lastly, we will test for Heterogeneity of Treatment Effect (HTE) based on age, gender, race/ethnicity, AML diagnosis (newly diagnosed vs. relapsed/refractory), and enrollment of caregiver using interaction terms in the mixed models (see HTE analysis plan). We

will utilize a similar strategy when comparing patient-reported depression (HADS-depression), anxiety (HADS-anxiety), PTSD symptoms (PTSD-Checklist), coping (Brief COPE), symptom burden (ESAS-r), and perception of centeredness of care (PPPC) between the two groups. The mixed models also permit inclusion of patients who only provide partial longitudinal data so that all available data are contributing to the analysis.

16.0.2 Aim 2

To assess whether primary PC is non-inferior to specialty PC for improving patient-clinician EOL communication: We will examine patient-report of discussing EOL care preferences with their clinicians 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?" (Yes/No). Although patients will complete this measure repeatedly during the study, we will use the final assessment either prior to death or at last follow-up assessment point (whichever comes first) for this analysis. We will compare differences between study groups in the rate of patients reporting "Yes" to this item using a binomial generalized linear mixed effects model with an identity link function, adjusting for any demographic and clinical factors that are imbalanced between the two groups (non-inferiority margin of 13%) and a single random effect for cluster. Utilizing a similar statistical approach, we will conduct an exploratory analysis comparing patient and caregiver prognostic understanding using the response to the following item of the PTPQ: "What is the likelihood that you will be cured of your leukemia?" Responses will be dichotomized as accurate versus inaccurate as done in prior studies. Although patients and caregivers will complete this measure repeatedly during the study, we will also use the final assessment either prior to death or at 24 weeks (whichever comes first) for this analysis.

16.0.3 Aim 3

To compare the effect of primary PC versus specialty PC on EOL outcomes for patients with AML: We will compare chemotherapy use (yes/no; non-inferiority margin 15%) using a binomial generalized linear mixed effects model with an identity link function, adjusting for any demographic and clinical factors that are imbalanced between the two groups. We will also explore differences in hospitalizations (yes/no), ICU admissions (yes/no), and hospice utilization (yes/no) in the last 30 days of life between the two study groups using mixed effect logistic regression models. We will explore differences in hospice length-of-stay between primary PC and specialty PC using linear mixed effects models adjusting for imbalances between the two groups.

16.0.4 Aim 4

To compare the effect of primary PC versus specialty PC on caregiver QOL and psychological distress: We will assess the non-inferiority of primary PC versus specialty PC on caregiver QOL

(CarGOQOL, non-inferiority margin 5 points), depression (HADS-Depression, non-inferiority margin 1.5 points), anxiety (HADS-anxiety, non-inferiority margin 1.5 point) symptoms at week-12 using linear mixed effects models. We will also utilize mixed models when differences between groups in these outcomes at multiple time points (i.e., baseline, weeks 2, 4, 12, and 24).

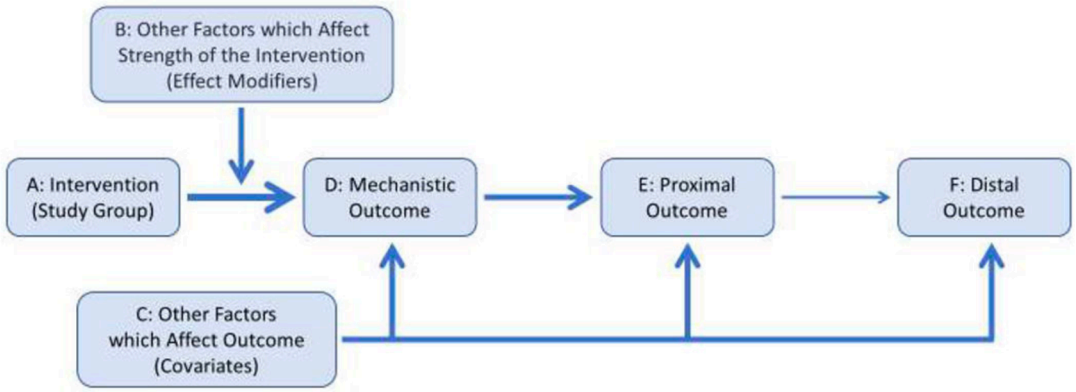
16.0.5 Aim 5

Qualitative analyses based on RE-AIM Quest: Trained study staff will conduct audio-recorded qualitative interviews with patients, caregivers, oncology and PC clinicians, and hospital leaders. Data analyses will co-occur with interview data collection to ascertain if thematic saturation (the point at which no new data are generated) has been achieved for each stratum (i.e., small, medium, or large leukemia programs). All interviews will be recorded, transcribed, and analyzed using NVivo 12 qualitative software. Two independent coders will analyze the interview content thematically, overseen by Dr. Park. Guided by RE-AIM, the coders will meet to develop the thematic framework and coding plan. Each interview will be coded twice. Interpretation and analysis of coded transcripts will follow the RE-AIM framework: 1) reach, 2) effectiveness, 3) adoption, 4) implementation, and 5) maintenance. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high level of reliability (kappa > 0.80) is established. Individual interview results will be analyzed by strata comparisons. After the dataset is complete, the study team will conduct independent expert reviews of the data prior to integration with quantitative data.

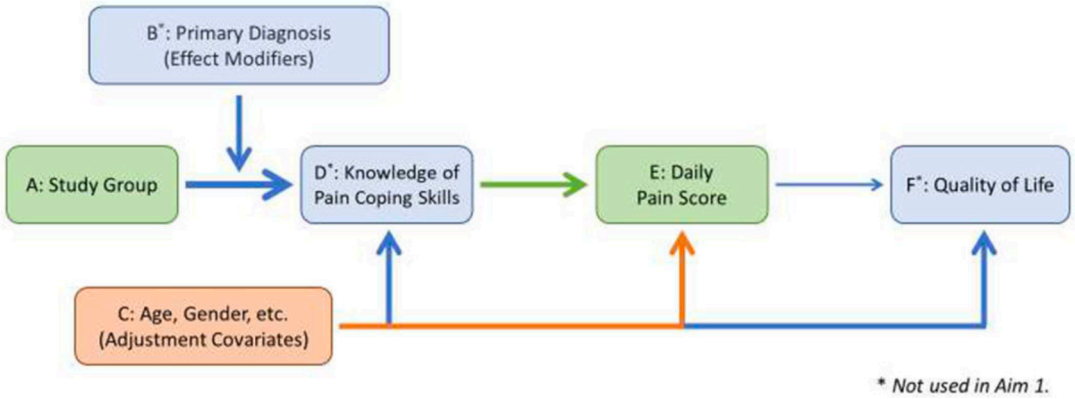
17 Causal Dag

Directed Acyclic Graph (DAG) is a graphical representation of causal relationships between variables. It is a useful visual tool for developing the statistical analysis plan for a randomized trial, and helps facilitate communication between statisticians and other investigators.

```
knitr::include_graphics("figures/F23_causal_dag1.png")
```




```
knitr::include_graphics("figures/F23_causal_dag2.png")
```



17.1 DAG with ggdag

Here is the package ggdag to build a DAG. The package dagitty is used to work with DAG logic.

But it seems really hard to use in the case.

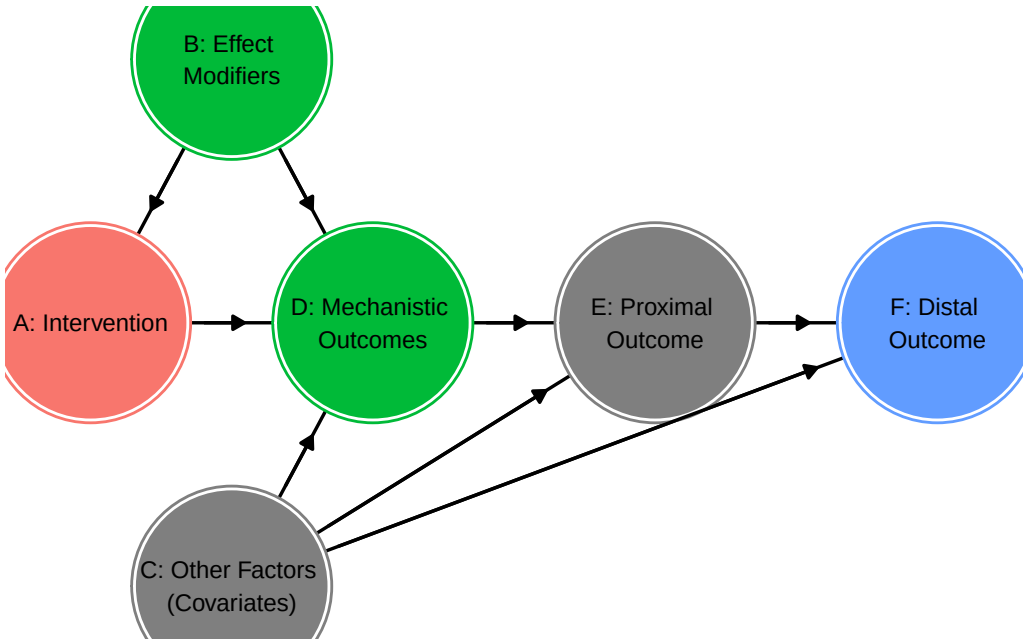
Here is the DAG for the example in the paper.

```
df_labels = data.frame(x = c(A = 1, D = 2, E = 3,
                             `F` = 4, B = 1.5, C = 1.5),
                       y = c(A = 0, D = 0, E = 0,
                             `F` = 0, B = 0.5, C = -0.5),
                       label = c("A: Intervention", "D: Mechanistic \nOutcomes",
                                 "E: Proximal \nOutcome",
                                 "F: Distal \nOutcome", "B: Effect \nModifiers",
                                 "C: Other Factors \n(Covariates)"))

dag <- dagify(`F` ~ E, E ~ D, D ~ A,
              A ~ B, D ~ B,
              `F` ~ C, E ~ C, D ~ C,
              latent = c("B", "D", "F"),
  exposure = "A",
  outcome = "F",
  coords = list(x = c(A = 1, D = 2, E = 3,
                      `F` = 4, B = 1.5, C = 1.5),
                y = c(A = 0, D = 0, E = 0,
                      `F` = 0, B = 0.5, C = -0.5)))

ggdag_status(dag,
             node_size = 35,
             edge_type = "link_arc",
             text = FALSE,
             stylized = TRUE,
             check_overlap = TRUE) +
  guides(fill = FALSE, color = FALSE) +
  geom_dag_edges(start_cap = ggraph::circle(15, 'mm'),
                 end_cap = ggraph::circle(17, 'mm')) +
  geom_text(data = df_labels,
            aes(x = x, y = y,
                label = label),
            inherit.aes = FALSE,
            size = 3) +
```

```
  theme_dag_blank()
```




```
  # expand_plot(expand_y = expansion(c(0, 0)))
```

17.2 DAG with `DiagrammeR`

Here is the DAG for the example in the paper.

```
flowchart2 <- DiagrammeR::grViz("
digraph {
  graph [layout = dot, rankdir = UD]

  # Define node styles
  node [shape = rectangle, style = filled, fontsize = 12, fontname = Helvetica]
  {# Nodes with colors
  edge [dir = none]
  A [label = 'A: Study Group'];
  invis1 [shape = none, style = invis]
  D [label = 'D*: Knowledge of Pain Coping Skills', fillcolor = lightblue]
```

```
  A -> invis1 [headclip=false]}

  E [label = 'E: Daily Pain Score'];
  F [label = 'F*: Quality of Life\\n(* Not used in Aim 1)', fillcolor = lightblue];
  {rank = same; A; invis1; D; E; F}
  # Draw arrows from A to D, E, and F
  invis1 -> D [tailclip=false]
  D -> E -> F

  B [label = 'B*: Primary Diagnosis\\n(Effect Modifiers)', fillcolor = lightblue];
  B -> invis1 [headclip=false] # helps position B above
  C [label = 'C: Age, Gender, etc.\\n(Adjustment Covariates)', fillcolor = lightsalmon];
  # Other arrows
  C -> {D, E, F}
}")


flowchart2
```

Part III

Study Methods

Description of the study design (e.g. parallel group randomized trial, case-control study, cohort study, etc.)

Randomization

Details in Section 18.1

Eligibility Criteria

List of eligibility and/or inclusion/exclusion criteria, Details in **?@sec-inclusion_exclusion**

Recruitment

Description of screening/enrolment/recruitment processes, Details in **?@sec-recruitment**

CONSORT

Description of patient flow (e.g. CONSORT diagram)

Analysis Population

Description of analysis population (e.g. intention to treat, per protocol, etc.)

Eligibility

Definitions of adherence/compliance, protocol deviations, loss-to-follow-up, adverse events, etc.

Adherence and Compliance

Protocol Deviations

Loss-to-follow-up

Adverse events

Other reasons

Timeline for Outcomes

Time points at which outcomes are measured Details in **?@sec-timeline**

Timeline for Analyses

Timing of final analyses (are all outcomes analysed collectively, or will short-term outcomes be analysed separately from long-term outcomes, etc.)

18 Randomization

This is a cluster randomized comparative effectiveness trial of primary PC versus specialty PC in 1150 patients with AML and their caregivers. Patients and their caregivers will be recruited from 20 sites. During phase 2, the 16 sites will be randomized to specialty PC versus primary PC stratified by percent minority population to ensure a balanced proportion of minority participants across the arms. We will do this using covariated constrained randomization. This will generate all possible randomization scenarios, and one such randomization will be chosen from the list of possible randomizations that ensure balance on this binary variable. Seven additional sites will be randomized at the beginning of the study, but the list of allocations will be kept by the DCC and not shared with the CCC. Should a site drop out, one site from the respective arm will be selected from the additional backup sites, whose randomization was already assigned prior to the beginning of Phase II.

As per the requirement of the funding agency, phase 1 of this study will include implementing study procedures at four participating sites (two primary PC sites and two specialty PC sites) prior to opening the study at the remaining 16 sites. Phase 1 will be conducted over the first 18 months of the study period and enable us to optimize study procedures prior to opening the study at the remaining 16 sites during phase 2.

18.1 Site Randomization

The four sites participating in Phase 1 will be randomized in 1:1 fashion without any stratification to specialty PC versus primary PC using a computer-generated randomization schema. The 16 sites participating in phase 2 will be randomized at the end of phase 1 in 1:1 fashion, stratified by percent minority (>=30% vs <30% minority) demographic to specialty PC versus primary PC using covariate constrained randomization.

18.2 Study Intervention and Comparator

We are comparing two evidenced-based interventions, a primary PC and a specialty PC intervention in patients with AML and their caregivers. The PC domains addressed with both interventions are identical and based on our prior studies (Table 3). While the PC domains in both interventions are the same, the approach by which clinicians utilize the strategies will differ based on clinician specialty (i.e., oncology versus PC).

18.2.1 Specialty PC Intervention

All participating specialty PC clinicians will undergo training to ensure that the provision of services is consistent across study sites.. Prior to attending the training, the lead PC clinicians will review the specialty PC intervention guide. The lead PC clinicians will then train all participating PC clinicians at their site using the same training approach. Prior to the study start, all participating PC clinicians will review the specialty PC intervention guide, attend the site specialty PC training, and read required papers on the specialty PC model. Upon completion, trainees will complete a formal, post-training skills assessment (Section 9.3: Fidelity of study design, method, and intervention). Lead specialty PC clinicians will also be responsible for training any new clinicians at their sites using the same training approach. We will also conduct refresher trainings every six weeks during the first year of participant enrollment and then every 12 weeks thereafter with specialty PC clinicians.. PC clinicians will also document patient encounters in the electronic health record (EHR) of their respective institutions using a study specific template and complete a weekly electronic survey via REDCap to note the topics addressed during the visits for hospitalized patients and whether the caregiver was present.

Sites randomized to specialty PC will have their PC clinicians (physician or advance practice provider) see patients within three business days of enrollment. The PC clinicians will follow patients throughout their hospitalization for chemotherapy, seeing them at least twice per week. Patients and PC clinicians will be permitted to initiate additional visits as needed. PC clinicians will also follow patients during subsequent hospitalizations until death (or end of study period for those who are alive), with a minimum of two visits per week. Outpatient PC visits are not required. Although specialty PC is practiced by multidisciplinary clinicians, most inpatient practices are staffed predominantly by physicians and advanced practice providers. Study PC clinicians may involve additional clinicians (e.g., social workers, pastoral care) in the patient's care, but these visits will not replace the required twice weekly intervention visits.

18.2.2 Primary PC Comparator

We will conduct a half-day in-person training at each site randomized to primary PC (or over video due to the COVID-19 pandemic). The MGH investigative team will lead the training sessions at each site in collaboration with the sites' specialty PC clinicians. We will ask oncology clinicians to review the primary PC intervention guide prior to attending the training. During the training, the oncology clinicians will have the opportunity to practice new skills and receive feedback in a supportive environment. Upon completion, trainees will complete a formal, post-training skills assessment (**?@sec-fidelity**). We will also video record the training to ensure it is available for oncology clinicians who miss the initial training session. We expect the leukemia practices at each site will have staff turnover and new hires, thus the training will be made available on an annual basis (over video) throughout the study period.

We will also conduct refresher trainings every six weeks during the first year of participant enrollment and then every 12 weeks thereafter with the leukemia clinicians.

Prior to the study start, all participating oncology clinicians will review the intervention guide, attend the primary PC training, and read several papers highlighting the PC needs of patients with AML and their caregivers. We will also ask oncology clinicians to document the PC domains addressed during patient encounters in the EHR using a study specific template. Oncology clinicians will also complete a weekly electronic survey through REDCap for hospitalized patients to note the PC topics addressed and whether the caregiver was present for clinical encounters.

18.2.3 Table3

```
knitr::include_graphics("figures/F30_table3.png", dpi = 100)
```

≈		
Domains	**Elements**	**Strategies**
Therapeutic relationship	• Understanding the patient and caregiver experience • Building trust with the patient and caregiver	• 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 leukemia diagnosis • Develop trust and credibility with patients and caregivers by providing reassurance and outlining parameters of communication
Symptom management	• Preparing for symptoms • Assessing and treating symptoms • Providing referral for symptom management	• Clarify the symptoms that patients will likely experience and offer reassurance about the methods of reporting and treating symptoms • Elicit existing and new symptom concerns • Referrals for mental health, integrative medicine, and spiritual support as needed
Coping with illness	• Reviewing and validating prior coping efforts • Discussing different methods of coping • Supporting caregiver coping • Providing referral for additional support	• Recognize that patients and caregivers bring their own expertis in coping to the current circumstance based on prior experience • Introduce strategies to help improve adjustment and coping • 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)
Prognostic awareness and illness understanding	• Exploring goals and values • Assessing and informing patient expectation of prognosis • Facilitate living with prognostic uncertainty • Conducting separate conversations with caregivers	• Assess patient's hopes and expectations for treatment and futur to clarify the patient's level of prognostic awareness • Recognize that illness understanding often vacillates between more and less realistic expectations and work to improve prognostic awareness • Acknowledge difficulty living with prognostic uncertainty • Discuss strategies to help patients cope with uncertain prognosis • Include both patients and caregivers in conversations about prognosis and illness understanding when possible
Treatment decision-making	• Assessing patient values in treatment decision-making • Discussing treatment considerations • Supporting treatment decisions	• Elicit information from patients and caregivers regarding their decision-making style, quality versus quantity of life concerns, and life goals • Provide support for patients and caregivers to understand the efficacy and risks and benefits associated with leukemia treatment • Clarify misunderstandings about treatment, support patient decision-making, and freedom to change course
EOL care	• Discussing EOL care options • Supporting caregivers in EOL care coordination and grief support	• Discuss/review selection of healthcare proxy, determination of resuscitation preferences, transition to hospice care, and location of death • Determine available resources for EOL care and whether it is appropriate for patients to receive care in the home or other settings. Provide referral for grief support for caregivers.

19 Fidelity of Design

We are taking several steps to ensure the fidelity of our study design, training, and intervention delivery as noted in the Table 4 Section 19.0.1. To ensure the fidelity of our study design, we are implementing an evidence-based PC intervention, measuring the PC domains addressed in both study groups using clinician surveys, and monitoring the extent of contamination between groups. We will employ rigorous training procedures for all study personnel, as well as hold monthly video conferences with the site PIs and CRCs. To ensure the fidelity of intervention delivery, the DCC will generate primary and specialty PC fidelity reports based on the clinicians' electronic surveys summarizing the PC domains addressed during clinical encounters. The MGH investigative team will review the intervention fidelity reports to ensure conformity between sites in addressing the domains and topics as specified by the guide. Based on these reviews, the study team will provide feedback to individual clinicians to ensure they are delivering the interventions in a consistent fashion.

19.0.1 Table 4: Fidelity of Study Design, Methods, and Intervention

```
knitr::include_graphics("figures/F37_table4_fidelity.png",
  dpi = 100)
```

Table 4: Study Fidelity		
Component	**Steps Taken to Ensure Fidelity**	**Fidelity Ass**
Study Design	• Interventions based on a well-defined conceptual model and systematic review of literature • Standard intervention dose with clear feasibility data based on prior work • Minimal cross-contamination given lack of specialty PC involvement for patients with AML	• Utilize evi interventic • Monitor in surveys do during visi • Measure s randomize initiatives
Training	• Use of a specialty and primary PC intervention guides • Initial training of site PIs on study protocol • Initial training of site CRCs on study procedures • Site-PI led training of PC clinicians for specialty PC sites • Study team led training of oncology clinicians for primary PC sites • Annual booster training for study clinicians • Monthly video calls with study team	• Require st guide • Assess site • Assess site training • Assess PC training • Assess onc after traini • Assess cli training • Review stu
Intervention Delivery	• PC intervention guides with standardized content • Electronic surveys to record the content and topics that specialty PC clinicians addressed during visits • Electronic surveys to record content and topics that primary PC (i.e., oncology) clinicians addressed during visits	• Ensure nev interventic • The invest electronic • The invest electronic

20 Study Measures

Participant Self-Report Assessments: We selected measures based on our prior studies and the theoretical framework of delivering PC, in which the care domains aim to improve patients' quality of life (QOL), illness understanding, coping, end-of-life (EOL) communication, and caregiver outcomes (see Table 5). Patients will complete self-report assessments at baseline, weeks 2 (± 4 days), 4 (± 7 days), 12 (± 7 days), and 24 (± 7 days) from enrollment. Caregivers will complete self-report assessments at baseline, weeks 4 (± 7 days), 12 (± 7 days), and 24 (± 7 days) from enrollment. All measures have strong psychometric properties, responsiveness to change, and have been validated in this population. Furthermore, all measures are available in English and Spanish; we are also translating them into Simplified Chinese, Traditional Chinese, Tagalog, Arabic, French, Vietnamese, Korean, Italian, Portuguese, and Haitian Creole. Participants who complete the Week 24 self-report assessment will receive a Certificate of Appreciation from the research team for their participation.

20.0.1 Patient Measures

- **Demographics:** Age, race, ethnicity, gender identity, marital status, religion, education, and income.
- **Functional Assessment of Cancer Therapy–Leukemia (FACT-Leukemia):** A 44-item QOL measure that assesses physical, social, emotional, and functional well-being, as well as leukemia-specific symptoms (Cella et al. 2012).
- **Post-traumatic Stress Checklist–Civilian Version:** A 17-item PTSD Checklist evaluating the severity of PTSD symptoms (Smith et al. 1999).
- **Edmonton Symptom Assessment Scale (ESAS-R):** A 10-item instrument to assess various symptoms relevant to patients with AML.
- **Patient Perception of Patient-Centeredness of Care (PPPC):** A 14-item measure of patients' perceptions of the centeredness of care.

20.0.2 Caregiver Measures

- **Demographics:** Age, race, ethnicity, gender identity, religion, education, and relationship to the patient.
- **Caregiver Oncology QOL Questionnaire (CARGOQOL):** A 29-item caregiver QOL measure (Minaya et al. 2012).

- **Caregiver Reaction Assessment (CRA):** A 24-item measure of caregiver burden (Given et al. 1992).

20.0.3 Patient and Caregiver Measures

- **Hospital Anxiety and Depression Scale (HADS):** A 14-item measure with depression and anxiety subscales (Zigmond and Snaith 1983).
- **Brief COPE:** A measure assessing various coping strategies (Carver 1997).
- **Prognostic Awareness Impact Scale (PAIS):** A tool to assess prognostic understanding and communication regarding prognosis and EOL care.

20.0.4 EOL Care

EOL care data will be extracted from the electronic health record (EHR) at participating institutions. We will collect data on chemotherapy usage, hospitalizations, ICU admissions, and hospice utilization in the last 30 days of life, reflecting that patients with AML generally receive all of their medical care at their treating institution.

```
knitr::include_graphics("figures/F38_table5.png", dpi = 100)
```

Table 5. Study Outcomes			
Primary or Secondary	**Name of Outcome**	**Measure**	
Patient Outcomes			
Primary	QOL	FACT-Leukemia	Baseline,
Secondary	Depression symptoms	HADS-Depression Subscale	Baseline,
Secondary	Anxiety symptoms	HADS-Anxiety Subscale	Baseline,
Secondary	PTSD symptoms	PTSD Checklist-Civilian Version	Baseline,
Secondary	EOL communication	PAIS	Weeks 4,
Secondary	EOL care delivery	EHR review	Last 30 da
Exploratory	Prognostic understanding	PAIS	Weeks 4,
Exploratory	Coping	Brief COPE	Baseline,
Exploratory	Symptom burden	ESAS-revised	Baseline,
Exploratory	Acceptability and satisfaction with PC	PPPC	Weeks 4,
Caregiver Outcomes			
Secondary	QOL	CarGOQOL	Baseline,
Secondary	Caregiving burden	CRA	Baseline,
Secondary	Depression symptoms	HADS-Depression Subscale	Baseline,
Secondary	Anxiety symptoms	HADS-Anxiety Subscale	Baseline,
Exploratory	EOL communication	PAIS	Weeks 4,
Exploratory	Prognostic understanding	PAIS	Weeks 4,
Exploratory	Coping	Brief COPE	Baseline,

21 Sample Size

Our study is powered to assess multiple the primary outcome and multiple secondary outcomes as shown in Table 6. We chose non-inferiority margins below the threshold of what is considered a clinically significant based on the differences seen in our prior specialty PC trials. The primary endpoint of this study is to establish that primary PC is non-inferior to specialty PC in patient-reported QOL at week 12. As noted in table Table 1, in our prior study of specialty PC versus usual care in patients with AML, we found clinically and statistically significant differences between study groups at week-2 that persisted at week-12. Thus, we have chosen to power our study at week-12, which will enable us to conduct a longitudinal analysis examining the effect of the intervention over the first 12 weeks. In our prior study, we observed an 11-point difference in QOL between the two groups at week-12, favoring the specialty PC group. Thus, we chose a conservative non-inferiority margin of five points (less than 50% of the previously observed difference with specialty PC) which does not reach the threshold for clinically meaningful difference in QOL (six-point difference in FACT-Leukemia). With each of the 20 sites enrolling approximately 57-58 patients (total N=1150 patients), we will have >90% power to establish the non-inferiority of primary PC compared to specialty PC with a one-sided alpha of 0.025 and a non-inferiority margin of five points (assuming an intra-cluster correlation coefficient (ICC) = 0.03 and missing data rate of 20% at week 12). Notably, in our prior multi-site trial, the rate of missing data at week 12 was only 14%. Please note, we will be using a one-sided alpha of 0.025 for this proposed non-inferiority trial.

```
knitr::include_graphics("figures/F33_table6.png")
```

Table 6: Power and Sample Size Calculation based on a one-sided alpha of 2.5%

Primary or Secondary	Outcome Measure	Non-inferiority Margin	Missing Data	Power ICC=0.01	Power ICC=0.03	Power ICC = 0.05
Patient Outcomes (N = 1150 patients recruited from 20 clusters)						
Primary	QOL (FACT-Leukemia)	5 points	20%	>99%	94%	85%
Secondary	Depression (HADS-Depression)	1.5 points	20%	98%	89%	78%
Secondary	Anxiety (HADS-Anxiety)	1.5 points	20%	99%	93%	83%
Secondary	PTSD (PTSD Checklist)	3 points	20%	>99%	95%	86%
Secondary	EOL communication (PTPQ)	13%	< 5%*	98%	89%	78%
Secondary	Chemotherapy in the last 30 days of life	15%	< 5%**	98%	85%	73%
Caregiver Outcomes (N = 575 caregivers recruited from 20 clusters)						
Secondary	QOL (CarGOQOL)	5 points	20%	98%	92%	85%
Secondary	Caregiving burden (CRA)	5 points	20%	93%	82%	73%
Secondary	Depression (HADS-Depression)	1.5 points	20%	95%	86%	78%
Secondary	Anxiety (HADS-Anxiety)	1.5 points	20%	96%	89%	81%

* Patient-reported EOL communication is measured with the PTPQ at baseline, weeks 2, 4, 12, and 24. Analyses focus on last reported response to this item, and thus expected missing data rate is < 5%.
** Most patients with AML receive longitudinal care at our participating institutions and thus we expect to have < 5% missing data on EOL care delivery

Additionally, in a recent cluster randomized trial of primary PC for patients with advanced cancer, the estimated ICC was 0.03. However, we chose to be conservative in accounting for missing data and our ICC to ensure adequate power.

Sample size calculation or justification (either provided in full or summarized, with link to original source)

21.1 Subgroup analysis

21.2 Power

21.3 Multiple comparisons

Description of pre-planned subgroup analyses, power for these analyses, and planned multiple comparison adjustment procedures

22 Interim Analysis

Description of what interim analyses will be conducted at which time points, and what methods used to adjust significance levels due to the interim analysis

22.1 Stopping Guidelines

Details of any guidelines (e.g. safety, futility) for stopping the study early

22.2 Changes to Trial Design

Details of any changes to trial design due to interim analyses (e.g. enrolling more patients)

23 Data Information

23.0.1 Data Collection

We developed data collection tools, dictionaries, collection instructions, and the REDCap database with the DCC to ensure that we collect data systematically from all study participants. We are utilizing similar data collection strategies from our prior multi-site trials with low rates of missing data. We will make every effort to accommodate patient schedules and to collect patient-reported assessments during regularly scheduled visits or hospitalizations when possible. We will ask participants to provide their email address to allow us to send study assessments using a secure electronic system when patients do not have a scheduled, in-person appointment within the follow-up time points. Participants who opt out of using secure email can either receive paper copies of the assessment by mail or complete the questionnaire verbally over the telephone. The participant-reported assessments take approximately 15 minutes to complete. We will also track the method of assessment completion. Non-English-speaking participants will have the option of completing follow-up assessments in-person as a first preference, over the telephone with the assistance of an interpreter, or via mail. Study staff who are fluent in the participant's language may administer assessments via telephone or via institution-approved video technology. Non-English assessments will not be administered via email as this is not possible with REDCap.

23.0.2 Data Obtained from EHR

In addition to collecting EOL care data from the EHR, we will also collect baseline clinical, disease, and treatment information including: ECOG performance status, clinical comorbidities (Sorror Comorbidity Index (Sorror and Appelbaum 2013)), AML type, date of diagnosis, and disease risk (Disease Risk Index (Armand et al. 2014), cytogenetics, and mutations). We will collect data on AML recurrence and additional treatments, including stem cell transplantation.

23.0.3 Data on Addressing PC Domains

All participating clinicians will complete a brief REDCap survey weekly during study patient's hospitalizations. This survey assesses PC domains and strategies addressed during clinical encounters. The survey is intentionally brief and takes approximately two minutes to complete

to reduce burden on busy clinicians. In our prior studies, clinicians completed 100% of these weekly surveys. We will use the identical study procedures to ensure documentation of the PC domains addressed in the proposed trial. Specifically, prior to the study start, all participating PC will be trained on the use of the REDCap survey and the importance of entering these data. The site CRC will send a secure email with a link to the REDCap system on weekly basis. If clinicians do not complete the REDCap entry within 48 hours, they will receive a reminder email copied to the site PI.

23.0.4 Data Collection Based on RE-AIM Quest Framework

We will utilize the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) QuEST (Qualitative Evaluation for Systematic Translation) framework to systematically to assess key dimensions of intervention implementation to enable future dissemination in real-world clinical settings. We will audio record the monthly video conferences with participating sites and create a log describing the barriers and facilitators for primary and specialty PC implementation and adoption and use this log to develop the semi-structured interview guides for the qualitative interviews with key informants. Due to the potential impact of the size of the leukemia program on challenges pertaining to implementation and adoption, we will conduct qualitative interviews stratified by the size of the leukemia program at participating sites. For each key informant group, we will interview 30 individuals, including 10 from each size stratum (small, medium, or large leukemia program). Specifically, we will conduct interviews with: - 1) patients with AML receiving specialty PC and caregivers; - 2) patients with AML receiving primary PC and caregivers; - 3) oncology clinicians; - 4) PC clinicians; - 5) hospital leaders to identify facilitators and barriers to the adoption, implementation, and maintenance of primary PC and specialty PC.

We will collect the following data: - Reach: We will assess: - 1) the number of eligible patients and caregivers who were approached about the study; - 2) number of patients enrolled, and characteristics of refusers and enrollees; - 3) reason for refusal. We will also utilize the qualitative interviews with patients, caregivers, oncology and PC clinicians to assess recruitment and retention facilitators and barriers and discuss how they can be addressed.

- Effectiveness: We will evaluate effectiveness based on the comparative effectiveness of primary PC versus specialty PC on participant-reported outcomes. Additionally, we will analyze qualitative interviews of patients, caregivers, oncology and PC clinicians about the acceptability and perceived effective features of primary PC and specialty PC.
- Adoption: To examine adoption, we will assess oncology and PC clinician participation rates (i.e., % of eligible clinicians completing training requirements for specialty and primary PC). We will also quantitatively summarize proportion of oncology and PC clinicians completing the visit note template and REDCap surveys. We will solicit feedback during our qualitative interviews with oncology and PC clinicians, as well as hospital leaders related to primary PC and specialty PC implementation logistics and barriers

to integration of these care models into clinical practice. In qualitative interviews with patients and caregivers, we will focus on individual factors that may have affected their participation and their desire to engage with primary or specialty PC to address their needs.

- Implementation: We will assess implementation based on fidelity to the protocol and intervention delivery (see Fidelity of Study Design, Methods, and Intervention). We will review and quantitatively summarize data on documentation of PC domains addressed during clinical encounters using the EHR. We will also review the REDCap surveys from participating clinicians longitudinally to assess changes in the patterns of PC domains addressed throughout the project period. We will also explore contamination, as noted previously, by recording patients' use of specialty PC services in sites randomized to primary PC. In qualitative interviews with patients, caregivers, oncology and PC clinicians, we will assess overall satisfaction with the specialty and primary PC interventions and focus on ideas for intervention modification and adaptation to maximize implementation into practice.
- Maintenance: We will assess the comparative effectiveness of specialty PC versus primary PC on EOL care delivery to assess maintenance of intervention effects at the EOL. During qualitative interviews with patients and caregivers, we will explore whether modification to the specialty and primary PC interventions are needed. With the oncology and PC clinicians, as well as hospital leaders, we will explore barriers and facilitators to the specialty and primary PC maintenance and integration into standard oncology practice. Throughout the study, we will also utilize our Dissemination and Implementation stakeholder group meetings on bi-annual basis to discuss barriers and facilitators for primary and specialty PC sustainability (see Section H Engagement Approach)

23.1 Data and Specimen Banking

Not applicable

23.2 Data Management

23.2.1 Data Storage

All participant information and study source documents will remain confidential and be scanned and stored on secure institutional computers and in REDCap. Data abstracted from the EHR in Section 5.4.2 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 study staff with planning assistance from the Data Coordinating Center (DCC).

See **?@sec-sample_size** for Sample Size and Power calculations.

23.2.2 Data Coordinating Center (DCC) and Data Quality Checks

The DCC will lead the design and implementation of the statistics, informatics, and data management systems for the study. The DCC will work with the investigative team to develop, implement, and maintain systems for a central data repository. The DCC will be responsible for data cleaning and manipulation, generating monthly data collection and intervention fidelity reports, and providing necessary data for the Data Safety and Monitoring Board (DSMB). The DCC will be responsible for the following:

- Multi-site data repository: The data repository will contain all raw data from participating sites. The raw data will be organized into the master datasets that is ready for analysis based on established data standards and SDEs.
- Monthly quality reports: The monthly quality reports will include the key study-specific metrics that will track essential progress measures such as enrollment, data quality, and adherence to the primary and specialty PC interventions.
- Document library: All data collection protocols, policies, and procedures will be organized in a password-protected searchable online library for use by study personnel to assure the integrity of data collection procedures.
- Software and results library: All computer code that is used to construct datasets and analyses will be archived with version control so that all analyses and reports can be exactly duplicated at any time.
- Training materials and resources: Training procedures and manuals will be developed for all data collection procedures based on the corresponding data collection protocols.

23.2.2.1 REDCap

The DCC Informatics systems will be programmed and maintained by the DCC using REDCap. The REDCap database will be managed centrally in the DCC and will be accessible via the internet at remote sites. The DCC will utilize REDCap to generate the monthly data collection and intervention fidelity reports under the supervision of the DCC investigative team. They will also prepare specialized quality control reports as needed.

23.2.2.2 Pre-Specification of Research Projects

All publications or ancillary studies will be pre-planned in collaboration with the DCC. The DCC will evaluate the feasibility of proposed studies and will assist in development of statistical analysis plans.

23.2.3 Data Monitoring

The DCC will assure data completeness, adherence to study protocols, and timelines by providing monthly quality reports for site PIs and the MGH investigative team. These monthly reports will include the key metrics including enrollment, data quality (i.e., missing data rates), and adherence to the primary and specialty PC interventions. The content of these monthly reports will be used by the study team to identify and correct problems as they occur. All study data will be collected through a REDCap central data repository at the University of Colorado. Data will be exported directly to a server behind the firewall for cleaning, manipulation, and analysis. Only the DCC team will have access to the data during the study. The DCC will generate the required data reports for the DSMB.

23.2.4 Data Security

Participant data will be collected at each participating institution 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.

Participants' responses to survey questions will remain confidential. In addition, as stated previously, all study staff at all participating sites will undergo an extensive training on study procedure as well as data management to ensure data security and maintaining of confidentiality.

23.3 Data Processing

23.4 Data Extraction

24 Missing Data

Description of sources and magnitudes of missing data

As in our prior PC trials, we will utilize rigorous methodology in reporting reasons for dropout and missing data during the study period including: 1) patient death; 2) inability to complete the study due to illness; 3) transfer of care; 4) withdrawal of consent; and 5) unable to contact for follow-up. The investigative team will review missing data rates for all participating sites to address any discrepancies in missing data compared to prior studies and to ensure rigorous retention and follow-up procedures. We will use the ITT 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. We will include all available data for analysis of primary and secondary outcomes. Some patients may have missing covariate or outcomes data. Zhao and Ding showed that greater precision and efficiency can be achieved by using a single imputation (such as mean imputation) plus a missing variable indicator for each missing covariate in regression models for analysis of randomized trials, even when data are missing not at random (MNAR). We will use this approach for inclusion of covariates in all mixed models. Missing outcome data will not be imputed in the primary analysis; however, patients can contribute any number of time points in the mixed regression model (i.e., completion of all time points is not required) and the maximum likelihood–based estimates are valid if data are missing at random. Additional sensitivity analyses may also be conducted in handling missing data (e.g., employing pattern mixture modeling or joint modeling approaches), under the direction of the DCC.

24.1 Missing Patterns

Description of how missing data patterns will be presented/summarized (may be helpful to have a table shell or draft CONSORT-style diagram)

24.2 Missing Strategies

Description of contingency plans for handling missing data in analysis

25 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. Participants who withdraw,or transfer care within 30 days of enrollment will still be included in the analysis We will also recruit new patients for each patient withdrawn to ensure adequate study sample size. We will increase the total accrual goal within each cluster to account for patients who withdraw, or transfer care within 30 days of the study period.

25.1 Risks to Subjects

Given that this study is a palliative care study, 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 with AML 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.

25.2 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.

25.3 Reaction Management

We will obtain informed consent from all study participants. The consent 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 oncology 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 CRC will inform the site-PI. The site-PI will determine the need to involve psychiatry and take further action as deemed necessary.

25.4 Potential Benefits to Subjects

Patients with AML and their caregivers struggle with this difficult cancer diagnosis that significantly impacts their health and wellbeing, requires them to make difficult medical and EOL decisions, and carries substantial uncertainty about the future. Current cancer care models do not attend to or address these immense unmet PC care needs, which causes suffering for patients and their caregivers. While specialty PC has been shown to improve the outcomes and experience for patients with cancer, including AML, it will not be a feasible or widely adopted care model unless we demonstrate that it is the optimal way to support patients and their caregivers. The results of this study will definitively demonstrate whether primary PC is an effective alternative care model to specialty PC and provide the necessary data for health care settings to implement these care models. It is possible that study participants would benefit from the specialty PC and/or primary PC model of care.

25.5 Vulnerable Populations

Not applicable

25.6 Community-Based Participatory Research

Not applicable

25.7 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.

25.8 Recruitment Setting

Participants will be recruited for study participation across 20 sites. Patients will be approached for study participation in their private hospital room during their hospitalization for AML. Caregivers will be approached for study participation in-person in a private hospital room or over the telephone. For completion of follow-up assessments, participants can be approached on the inpatient unit in a private room, during a clinic visit in a private space, or over the telephone.

25.9 Local Number of Subjects

We anticipate that each site (including MGH) will recruit approximately 58 patients and up to 58 caregivers during the study period.

25.10 Provisions to Protect the Privacy Interests of Subjects

Participant data will be collected at each participating institution 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 downloaded by the DCC from REDCap. Participants' responses to survey questions will remain confidential.

25.11 Compensation for Research-Related Injury

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

25.12 Economic Burden to Subjects

We do not anticipate any financial burden on study participants. Specialty palliative care consultations are standard of care and will be covered under the cost of participants' hospitalizations. Patients will not be billed for palliative care visits.

26 Safety of Subjects

The study will have a data safety and monitoring board (DSMB).

26.1 Membership of the DSMB

The DSMB will be responsible for safeguarding the interests of participants in the proposed trial. To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB committee be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members will consist of three members with 1) experience in conducting multi-site PC clinical trials, 2) expertise in biostatistics, and 3) a thorough knowledge of clinical trial ethics and human subject protection issues. The statistician will chair the committee. The DSMB will be advisory to the investigative team. The study team will be responsible for promptly reviewing any DSMB recommendations and deciding how to respond.

26.2 Functional Organization of the DSMB

The initial meeting of the DSMB will occur during phase 1 of the trial. This meeting will be organizational and will provide advisory review of scientific and ethical issues relating to the study design and conduct and review of standard operating procedures for the role and function of the DSMB and the reporting obligations. Participants in this meeting will include all members of the DSMB, the MGH investigative team, and members of the DCC. Subsequent meetings will occur annually via video conference, to review randomization data, audits, conformance with informed consent requirements, verification of source documents, investigator compliance, as well as adverse events. These adverse events will be tracked for IRB submission as well. Per the DF/HCC IRB, study related adverse events are reported in real time, and study unrelated adverse events are reported at each continuing review.

26.3 Monitoring of Safety Data by the DSMB

- Unblinded Reporting: Safety information for this study will be reported to the committee in an unblinded manner. A statistical penalty will not be assessed for the ongoing

unblinded review of safety by the Committee. Unblinded data will not be released to the investigators unless necessary for safety reasons.

- Range of Safety Reporting to the DSMB: It is considered necessary for the purpose of monitoring the safety of the study that the committee review not only adverse events (AEs) and SAEs, but also other data that may reflect differences in safety between groups. This includes treatment retention rates and reasons for dropout.
- Recruitment reports: The DCC will generate recruitment and retention reports that will be made available to the DSMB committee
- Data Repository: The DCC will generate data collection and management reports (including rate of missing date) that will be made available to the DSMB committee.
- Serious Adverse Events: Given that this is a supportive care study in a population at risk for disease progression and death due to their medical condition (unrelated to the study procedures), we do not expect any SAEs to be related to the study. Thus, SAEs will not be reported to the DSMB, unless they are potentially related to study procedures.
- Non-Serious Adverse Events: At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase.
- Study Stopping Rules: If at any time during the course of the study, the committee judges that risk to subjects outweighs the potential benefits, the committee shall have the discretion and responsibility to recommend that the study be terminated. We do not, however, have a pre-specified stopping rule.
- Procedures to ensure confidentiality, preparation of reports, minutes, and recommendations: The DCC will prepare study reports and circulate them to the DSMB members at least two weeks before each regularly scheduled DSMB meeting. These reports will include overall study progress and safety data. A study team member will draft minutes of the DSMB meetings, working closely with the DSMB chair. Minutes will be circulated only to DSMB members for editing and final approval. At the conclusion of each DSMB meeting, the members will determine whether any changes in the conduct of the trial are recommended. In case of difference of opinion, majority vote will determine the DSMB recommendations. The DSMB chair will forward these recommendations to the MGH investigative team within two weeks of the DSMB meeting. The MGH investigative team will be responsible for sharing the DSMB recommendations with all study staff and investigators, and providing a report back to the DSMB within two weeks of the receipt of the report for any substantive DSMB recommendations

26.4 Monitoring of Data Quality by the DSMB

We will provide the DSMB with a yearly report on data quality and completeness, including total participant, number of ineligible patients registered, proportion of missing participant-reported outcomes, proportion of missing clinician surveys, number of participants lost to follow-up, and number of adverse events. These reports will be used by the DSMB committee to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Part IV

Statistical Analysis

Hypothesis testing framework (e.g. superiority, equivalence, non-inferiority), or description of alternative analytic framework (e.g. evaluation of a posterior in a Bayesian analysis, etc.)

Level of significance for primary hypotheses, including a description and rationale for any multiple comparisons adjustment or Type I error control procedures

Description of any decision-making rules based on confidence intervals, credible intervals, prediction intervals, Bayes' factors, or other alternative inferential methods

Description of how the results of any hypothesis tests (or alternative inferential methods) will be interpreted with respect to both the statistical hypotheses and scientific aims/objectives of the study

27 Descriptive Statistics

List of characteristics (e.g. demographic, clinical) to be summarized descriptively (e.g. "Table 1") Description of how these characteristics will be summarized descriptively (e.g. means/medians vs. N (%), tabular displays, graphical displays, etc.) Summarize follow-up time (e.g. average and total amount) and number of events

28 Analysis Methods

We will analyze HTE by testing for interaction effects between the two groups and the following variables: patient age (> 65 vs. < 65), gender (male vs. female), race/ethnicity (White vs. other; White vs. Black; White vs. Asian; Non-Hispanic white vs. Hispanic/Latino), AML diagnosis (newly diagnosed vs. relapsed/refractory AML), and enrollment of caregiver (yes vs. no). The interaction terms will be tested in the linear and logistic mixed effect models.. All HTE analyses are considered exploratory and hypothesis-generating. Prior studies have found that age, gender, and race can moderate the impact of specialty PC in patients with cancer. However, it remains unclear whether these factors would contribute to HTE of primary PC versus specialty PC. Lastly, since caregiver engagement may impact patient-outcomes, we will examine whether enrollment of a caregiver contributes to the HTE of specialty PC compared to primary PC. We chose to be conservative with our sample size estimate to account for HTE analyses for the primary endpoint of the study.

28.1 Adjustment for a Moderate Number of Clusters

Although generalized linear mixed models (GLMMs) have been shown to produce robust inference for cluster randomized trials with at least 10 clusters, sensitivity analyses using an appropriate small-sample adjustment will be carried out for all primary and secondary outcomes (Leyrat et al. 2018).

29 Additional Analysis

Description of any pre-planned sensitivity analyses and how they will be interpreted Description of pre-planned subgroup analyses, power for these analyses, and planned multiple comparison adjustment procedures Description of any additional post-hoc calculations or analyses (e.g. evaluating interaction/ modification effects, calculating mediation or local average treatment effects, evaluation of AUROC curves, etc.) If conducting any bootstrap analyses, a description of the sampling algorithm and number of iterations used If conducting any cross-validation procedures, a description of how the cross-validation is conducted (e.g. leave-one-out, train/validation/test, etc.)

30 Sensitivity Analysis

31 Exploratory Analysis

Description and justification for any pre-planned exploratory analyses and what methods will be used to conduct them.

Framework for conducting any unplanned exploratory analyses and how they will be integrated into the planned analysis

32 Simulation Study

If conducting a simulation, a description of the purpose of the simulation and its design (e.g. fully factorial, partially factorial, grid search, etc.)

Define the fixed and variable factors or parameters in the simulation, the estimands/targets of the simulation, and the performance measures to be estimated (with justifications of their relevance to the estimands/targets)

Description of the tabular and graphical presentations of simulation results and their interpretation

33 Software and Packages

List of statistical software (along with version numbers) to be used for each phase of the analysis; in the case of R or Stata, additionally list any requisite installed packages and their version numbers

```
sessionInfo()
```

```
#> Platform: aarch64-apple-darwin20
#> Running under: macOS 15.3.2
#>
#> Matrix products: default
#> BLAS:   /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRblas.0.dylib
#> LAPACK: /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRlapack.dylib
#>
#> locale:
#> [1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
#>
#> time zone: America/Denver
#> tzcode source: internal
#>
#> attached base packages:
#> [1] stats     graphics  grDevices utils     datasets  methods   base
#>
#> loaded via a namespace (and not attached):
#>  [1] compiler_4.4.1    fastmap_1.2.0     cli_3.6.3         tools_4.4.1
#>  [5] htmltools_0.5.8.1 rstudioapi_0.16.0 yaml_2.3.10       rmarkdown_2.28
#>  [9] knitr_1.48        xfun_0.48         digest_0.6.37     jsonlite_1.8.9
#> [13] rlang_1.1.4       evaluate_1.0.0
```

34 Other Information

Description of any additional planned analyses of the data (e.g. a safety analysis looking at adverse event rates for a Data Safety Monitoring Board,

Part V

Tables Functions

Example tables related to any of the conducted analyses; if possible including any available preliminary data

35 Tables

Example figures related to any of the conducted analyses; if possible including any available preliminary data.

36 Figures

All the function are explained in R documentation.

Example figures related to any of the conducted analyses; if possible including any available preliminary data.

37 Example

Part VI

Additional Information

38 Appencies

If necessary, appendices may be included (e.g. a full data dictionary, a copy of a Case Report Form, etc.)

39 Glossary

- **APP**: Advanced Practice Provider
- **AML**: Acute Myeloid Leukemia
- **CarGOQOL**: CareGiver Oncology Quality of Life questionnaire
- **CTMS**: Clinical Trials Management System
- **COVID-19**: Coronavirus Disease 2019
- **CRA**: Caregiver Reaction Assessment
- **DCC**: Data Coordinating Center
- **DF/HCC**: Dana-Farber/Harvard Cancer Center
- **ECOG**: Eastern Cooperative Oncology Group (Performance Status)
- **EHR**: Electronic Health Record
- **ESAS-R**: Edmonton Symptom Assessment Scale – Revised
- **FDA**: Food and Drug Administration
- **FACT-Leukemia** (or **FACT-Leu**): Functional Assessment of Cancer Therapy – Leukemia
- **GLMM**: Generalized Linear Mixed Model(s)
- **HADS**: Hospital Anxiety and Depression Scale
- **HTE**: Heterogeneity of Treatment Effect
- **ICU**: Intensive Care Unit
- **IPW**: Inverse Probability Weighting
- **IRB**: Institutional Review Board
- **ICC**: Intra-Cluster Correlation Coefficient
- **ITT**: Intention-To-Treat
- **MNAR**: Missing Not At Random
- **MGH**: Massachusetts General Hospital
- **NCI**: National Cancer Institute
- **NVivo 12**: Qualitative Data Analysis Software
- **PTPQ**: Patient-Reported measure for End-of-Life communication
- **PC**: Palliative Care
- **PI**: Principal Investigator
- **PPPC**: Patient Perception of Patient-Centeredness of Care
- **QOL**: Quality of Life
- **QuEST**: Qualitative Evaluation for Systematic Translation
- **REDCap**: Research Electronic Data Capture
- **RE-AIM**: Reach, Effectiveness, Adoption, Implementation, and Maintenance
- **SAE**: Serious Adverse Event

- **SOP**: Standard Operating Procedure
- **SCOPE-Leukemia**: Specialty Compared to Oncology Delivered Palliative Care for Patients with Acute Myeloid Leukemia

40 Addenda

Any additional analyses conducted that were not included in the SAP should be documented in an addendum, describing the purpose of the additional analysis, when it was conducted, and by whom

Part VII

References

References for any non-standard statistical methods used References (and locations) for any relevant protocols, standard operating procedures, or other documents cited in the SAP

You can browse the list of more than 8,500 Creative Commons CSL definitions in the CSL Project's central repository

Alibhai, S. M., H. Breunis, N. Timilshina, et al. 2015. "Quality of Life and Physical Function in Adults Treated with Intensive Chemotherapy for Acute Myeloid Leukemia Improve over Time Independent of Age." *Journal of Geriatric Oncology* 6: 262–71.

Alibhai, S. M., M. Leach, H. Kermalli, et al. 2007. "The Impact of Acute Myeloid Leukemia and Its Treatment on Quality of Life and Functional Status in Older Adults." *Critical Reviews in Oncology/Hematology* 64: 19–30.

Armand, P., H. T. Kim, B. R. Logan, et al. 2014. "Validation and Refinement of the Disease Risk Index for Allogeneic Stem Cell Transplantation." *Blood* 123: 3664–71.

Bakitas, M. A., T. D. Tosteson, Z. Li, et al. 2015. "Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial." *Journal of Clinical Oncology* 33: 1438–45.

Bakitas, M., K. D. Lyons, M. T. Hegel, et al. 2009. "Effects of a Palliative Care Intervention on Clinical Outcomes in Patients with Advanced Cancer: The Project ENABLE II Randomized Controlled Trial." *JAMA* 302: 741–49.

Bernacki, Rachelle, Joanna Paladino, Bridget A. Neville, et al. 2019. "Effect of the Serious Illness Care Program in Outpatient Oncology: A Cluster Randomized Clinical Trial." *JAMA Internal Medicine* 179: 751–59.

Blackhall, Lesley J., Patrick Read, George Stukenborg, and et al. 2016. "CARE Track for Advanced Cancer: Impact and Timing of an Outpatient Palliative Care Clinic." *Journal of Palliative Medicine* 19 (1): 57–63.

Bosshard, R., K. O'Reilly, S. Ralston, et al. 2018. "Systematic Reviews of Economic Burden and Health-Related Quality of Life in Patients with Acute Myeloid Leukemia." *Cancer Treatment Reviews* 69: 224–32.

Burnett, A. K., R. K. Hills, D. W. Milligan, et al. 2010. "Attempts to Optimize Induction and Consolidation Treatment in Acute Myeloid Leukemia: Results of the MRC Aml12 Trial." *Journal of Clinical Oncology* 28: 586–95.

Carver, C. S. 1997. "You Want to Measure Coping but Your Protocol's Too Long: Consider the Brief COPE." *International Journal of Behavioral Medicine* 4: 92–100.

Cella, D., S. E. Jensen, K. Webster, et al. 2012. "Measuring Health-Related Quality of Life in Leukemia: The Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) Questionnaire." *Value in Health* 15: 1051–58.

El-Jawahri, A. A., G. A. Steensma, D. P. LeBlanc, T. W. Fathi, A. T. Graubert, T. DeAngelo, D. J. Wadleigh, et al. 2015. "Health Care Utilization and End of Life Care for Older Patients with Acute Myeloid Leukemia." *Cancer*.

El-Jawahri, A. R., G. A. Abel, D. P. Steensma, et al. 2015a. "Health Care Utilization and End-of-Life Care for Older Patients with Acute Myeloid Leukemia." *Cancer* 121: 2840–48.

———, et al. 2015b. "Health Care Utilization and End-of-Life Care for Older Patients with

Acute Myeloid Leukemia." *Cancer*.

El-Jawahri, A., G. A. Abel, L. Traeger, et al. 2019. "Quality of Life and Mood of Older Patients with Acute Myeloid Leukemia (AML) Receiving Intensive and Non-Intensive Chemotherapy." *Leukemia* 33: 2393–2402.

El-Jawahri, A., A. M. Nelson, T. F. Gray, et al. 2020. "Palliative and End-of-Life Care for Patients with Hematologic Malignancies." *Journal of Clinical Oncology* 38: 944–53.

El-Jawahri, A., M. Nelson-Lowe, H. VanDusen, et al. 2018. "Patient-Clinician Discordance in Perceptions of Treatment Risks and Benefits in Older Patients with Acute Myeloid Leukemia." *The Oncologist*.

El-Jawahri, Areej R., Thomas LeBlanc, Hannah VanDusen, and et al. 2016. "Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial." *JAMA* 316 (20): 2094–2103.

El-Jawahri, Areej R., Leigh N. Traeger, Jennifer A. Greer, and et al. 2017. "Effect of Inpatient Palliative Care During Hematopoietic Stem-Cell Transplant on Psychological Distress 6 Months After Transplant: Results of a Randomized Clinical Trial." *Journal of Clinical Oncology* 35 (32): 3714–21.

El-Jawahri, Areej, Thomas W. LeBlanc, Linda J. Burns, and et al. 2018. "What Do Transplant Physicians Think about Palliative Care? A National Survey Study." *Cancer* 124 (21): 4556–66.

El-Jawahri, Areej, Thomas W. LeBlanc, Alison Kavanaugh, and et al. 2021. "Effectiveness of Integrated Palliative and Oncology Care for Patients with Acute Myeloid Leukemia: A Randomized Clinical Trial." *JAMA Oncology* 7 (2): 238–45.

Epstein, Ronald M., Paul R. Duberstein, J. J. Fenton, et al. 2017. "Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial." *JAMA Oncology* 3: 92–100.

Farsi, Z., N. D. Nayeri, and R. Negarandeh. 2012. "The Coping Process in Adults with Acute Leukemia Undergoing Hematopoietic Stem Cell Transplantation." *Journal of Nursing Research* 20: 99–109.

Ferrell, B. T., J. S. Temin, S. Alesi, E. R. Balboni, T. A. Basch, E. M. Firn, J. I. Paice, et al. 2016. "Integration of Palliative Care into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update." *Journal of Clinical Oncology*.

Fife, B. L., P. O. Monahan, R. Abonour, et al. 2009. "Adaptation of Family Caregivers During the Acute Phase of Adult BMT." *Bone Marrow Transplantation* 43: 959–66.

Ganzel, C., Z. Sun, L. D. Cripe, et al. 2018. "Very Poor Long-Term Survival in Past and More Recent Studies for Relapsed AML Patients: The ECOG-ACRIN Experience." *American Journal of Hematology*.

Gemmill, R., L. Cooke, A. C. Williams, et al. 2011. "Informal Caregivers of Hematopoietic Cell Transplant Patients: A Review and Recommendations for Interventions and Research." *Cancer Nursing* 34: E13–21.

Gerlach, C., B. Alt-Epping, and K. Oechsle. 2019. "Specific Challenges in End-of-Life Care for Patients with Hematological Malignancies." *Current Opinion in Supportive and Palliative Care* 13: 369–79.

Gheihman, G., C. Zimmermann, A. Deckert, et al. 2015. "Depression and Hopelessness in Patients with Acute Leukemia: The Psychological Impact of an Acute and Life-Threatening Disorder." *Psychooncology*.

Ghodraty-Jabloo, V., S. M. Alibhai, H. Breunis, et al. 2015. "Keep Your Mind Off Negative Things: Coping with Long-Term Effects of Acute Myeloid Leukemia (AML)." *Supportive Care in Cancer*.

Ghodraty-Jabloo, Vida, Shabbir MH Alibhai, Henriette Breunis, and Martine TE Puts. 2015. "One Day at a Time: Improving the Patient Experience During and After Intensive Chemotherapy for Younger and Older AML Patients." *Leukemia Research* 39 (2): 192–97.

Given, C. W., B. Given, M. Stommel, et al. 1992. "The Caregiver Reaction Assessment (CRA) for Caregivers to Persons with Chronic Physical and Mental Impairments." *Research in Nursing & Health* 15: 271–83.

Grover, S., K. Rina, P. Malhotra, et al. 2019. "Caregiver Burden in the Patients of Acute Myeloblastic Leukemia." *Indian Journal of Hematology and Blood Transfusion* 35: 437–45.

Hui, David, Ahmed Elsayem, Eduardo Bruera, and et al. 2010. "Availability and Integration of Palliative Care at US Cancer Centers." *JAMA* 303 (11): 1054–61.

Hui, David, Matthew Park, Di Zhang, and et al. 2015. "Attitudes and Beliefs Toward Supportive and Palliative Care Referral Among Hematologic and Solid Tumor Oncology Specialists." *The Oncologist* 20 (11): 1326–32.

Hui, D., N. Didwaniya, M. Vidal, et al. 2014. "Quality of End-of-Life Care in Patients with Hematologic Malignancies: A Retrospective Cohort Study." *Cancer* 120: 1572–78.

Jacobsen, P. B., I. J. Sadler, M. Booth-Jones, et al. 2002. "Predictors of Posttraumatic Stress Disorder Symptomatology Following Bone Marrow Transplantation for Cancer." *Journal of Consulting and Clinical Psychology* 70: 235–40.

Jacobsen, P. B., M. R. Widows, D. M. Hann, et al. 1998. "Posttraumatic Stress Disorder Symptoms After Bone Marrow Transplantation for Breast Cancer." *Psychosomatic Medicine* 60: 366–71.

Jia, M., J. Li, C. Chen, et al. 2015. "Post-Traumatic Stress Disorder Symptoms in Family Caregivers of Adult Patients with Acute Leukemia from a Dyadic Perspective." *Psychooncology* 24: 1754–60.

Kavalieratos, Dimitrios, Jane Corbelli, D. Zhang, et al. 2016. "Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-Analysis." *JAMA* 316: 2104–14.

Klepin, H. D., A. V. Rao, and T. S. Pardee. 2014. "Acute Myeloid Leukemia and Myelodysplastic Syndromes in Older Adults." *Journal of Clinical Oncology* 32: 2541–52.

LeBlanc, T. W., P. C. Egan, and A. J. Olszewski. 2018. "Transfusion Dependence, Use of Hospice Services, and Quality of End-of-Life Care in Leukemia." *Blood* 132: 717–26.

LeBlanc, T. W., and H. P. Erba. 2019. "Shifting Paradigms in the Treatment of Older Adults with AML." *Seminars in Hematology* 56: 110–17.

LeBlanc, Thomas W., and Areej El-Jawahri. 2015. "When and Why Should Patients with Hematologic Malignancies See a Palliative Care Specialist?" *Hematology. American Society*

of Hematology. Education Program 2015 (1): 471–78.

———. 2018. "Hemato-Oncology and Palliative Care Teams: Is It Time for an Integrated Approach to Patient Care?" *Current Opinion in Supportive and Palliative Care* 12 (4): 530–37.

Leyrat, C., K. E. Morgan, B. Leurent, et al. 2018. "Cluster Randomized Trials with a Small Number of Clusters: Which Analyses Should Be Used?" *International Journal of Epidemiology* 47: 321–31.

Loh, K. P., M. Abdallah, A. J. Kumar, et al. 2019. "Health-Related Quality of Life and Treatment of Older Adults with Acute Myeloid Leukemia: A Young International Society of Geriatric Oncology Review Paper." *Current Hematologic Malignancy Reports* 14: 523–35.

Lupu, Diane, American Academy of Hospice, and Palliative Medicine Workforce Task Force. 2010. "Estimate of Current Hospice and Palliative Medicine Physician Workforce Shortage." *Journal of Pain and Symptom Management* 40 (6): 899–911.

Minaya, P., K. Baumstarck, J. Berbis, et al. 2012. "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." *European Journal of Cancer* 48: 904–11.

Mundy, E. A., E. B. Blanchard, E. Cirenza, et al. 2000. "Posttraumatic Stress Disorder in Breast Cancer Patients Following Autologous Bone Marrow Transplantation or Conventional Cancer Treatments." *Behaviour Research and Therapy* 38: 1015–27.

Nissim, R., G. Rodin, A. Schimmer, et al. 2014. "Finding New Bearings: A Qualitative Study on the Transition from Inpatient to Ambulatory Care of Patients with Acute Myeloid Leukemia." *Supportive Care in Cancer* 22: 2435–43.

Nissim, R., C. Zimmermann, M. Minden, et al. 2013. "Abducted by the Illness: A Qualitative Study of Traumatic Stress in Individuals with Acute Leukemia." *Leukemia Research* 37: 496–502.

Paladino, Joanna, Rachelle Bernacki, Bridget A. Neville, et al. 2019. "Evaluating an Intervention to Improve Communication Between Oncology Clinicians and Patients with Life-Limiting Cancer: A Cluster Randomized Clinical Trial of the Serious Illness Care Program." *JAMA Oncology* 5: 801–9.

Papadopoulou, C., B. Johnston, and M. Themessl-Huber. 2013. "The Experience of Acute Leukaemia in Adult Patients: A Qualitative Thematic Synthesis." *European Journal of Oncology Nursing* 17: 640–48.

Reddy, S. K., K. Tanco, S. Yennu, et al. 2019. "Integration of a Mandatory Palliative Care Education into Hematology-Oncology Fellowship Training in a Comprehensive Cancer Center: A Survey of Hematology Oncology Fellows." *Journal of Oncology Practice* 15: e934–41.

Rodin, G., D. Yuen, A. Mischitelle, et al. 2013. "Traumatic Stress in Acute Leukemia." *Psycho-Oncology* 22: 299–307.

Schenker, Yael, D. White, M. Rosenzweig, et al. 2015. "Care Management by Oncology Nurses to Address Palliative Care Needs: A Pilot Trial to Assess Feasibility, Acceptability, and Perceived Effectiveness of the CONNECT Intervention." *Journal of Palliative Medicine* 18: 232–40.

Schlenk, R. F., C. Muller-Tidow, A. Benner, et al. 2017. "Relapsed/Refractory Acute Myeloid Leukemia: Any Progress?" *Current Opinion in Oncology* 29: 467–73.

Smith, M. Y., W. Redd, K. DuHamel, et al. 1999. "Validation of the PTSD Checklist-Civilian Version in Survivors of Bone Marrow Transplantation." *Journal of Traumatic Stress* 12: 485–99.

Sorror, M. L., and F. R. Appelbaum. 2013. "Risk Assessment Before Allogeneic Hematopoietic Cell Transplantation for Older Adults with Acute Myeloid Leukemia." *Expert Review of Hematology* 6: 547–62.

Temel, J. S., J. A. Greer, A. El-Jawahri, et al. 2017. "Effects of Early Integrated Palliative Care in Patients with Lung and GI Cancer: A Randomized Clinical Trial." *Journal of Clinical Oncology* 35: 834–41.

Temel, J. S., J. A. Greer, A. Muzikansky, et al. 2010. "Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer." *New England Journal of Medicine* 363: 733–42.

Temel, Jerome S., Jeanne A. Greer, Areej El-Jawahri, et al. 2016. "Effects of Early Integrated Palliative Care in Patients with Lung and GI Cancer: A Randomized Clinical Trial." *Journal of Clinical Oncology*.

Vey, N. 2020. "Low-Intensity Regimens Versus Standard-Intensity Induction Strategies in Acute Myeloid Leukemia." *Therapeutic Advances in Hematology* 11: 2040620720913010.

Walter, R. B., and E. H. Estey. 2020. "Selection of Initial Therapy for Newly-Diagnosed Adult Acute Myeloid Leukemia: Limitations of Predictive Models." *Blood Reviews*, 100679.

Wiese, M., and N. Daver. 2018. "Unmet Clinical Needs and Economic Burden of Disease in the Treatment Landscape of Acute Myeloid Leukemia." *American Journal of Managed Care* 24: S347–55.

Zigmond, A. S., and R. P. Snaith. 1983. "The Hospital Anxiety and Depression Scale." *Acta Psychiatrica Scandinavica* 67: 361–70.

Zimmermann, C., N. Swami, M. Krzyzanowska, et al. 2014. "Early Palliative Care for Patients with Advanced Cancer: A Cluster-Randomised Controlled Trial." *Lancet* 383: 1721–30.

Zimmermann, C., D. Yuen, A. Mischitelle, et al. 2013. "Symptom Burden and Supportive Care in Patients with Acute Leukemia." *Leukemia Research* 37: 731–36.

Zittoun, R., S. Achard, and M. Ruszniewski. 1999. "Assessment of Quality of Life During Intensive Chemotherapy or Bone Marrow Transplantation." *Psycho-Oncology* 8: 64–73.