SUPPLEMENTARY APPENDIX

Randomized controlled trial of geriatric consultation *versus* standard care in older adults with hematologic malignancies

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Supplemental File 1: Study Protocol

Patient-Centered Care for the Older Adult with Hematologic Malignancy

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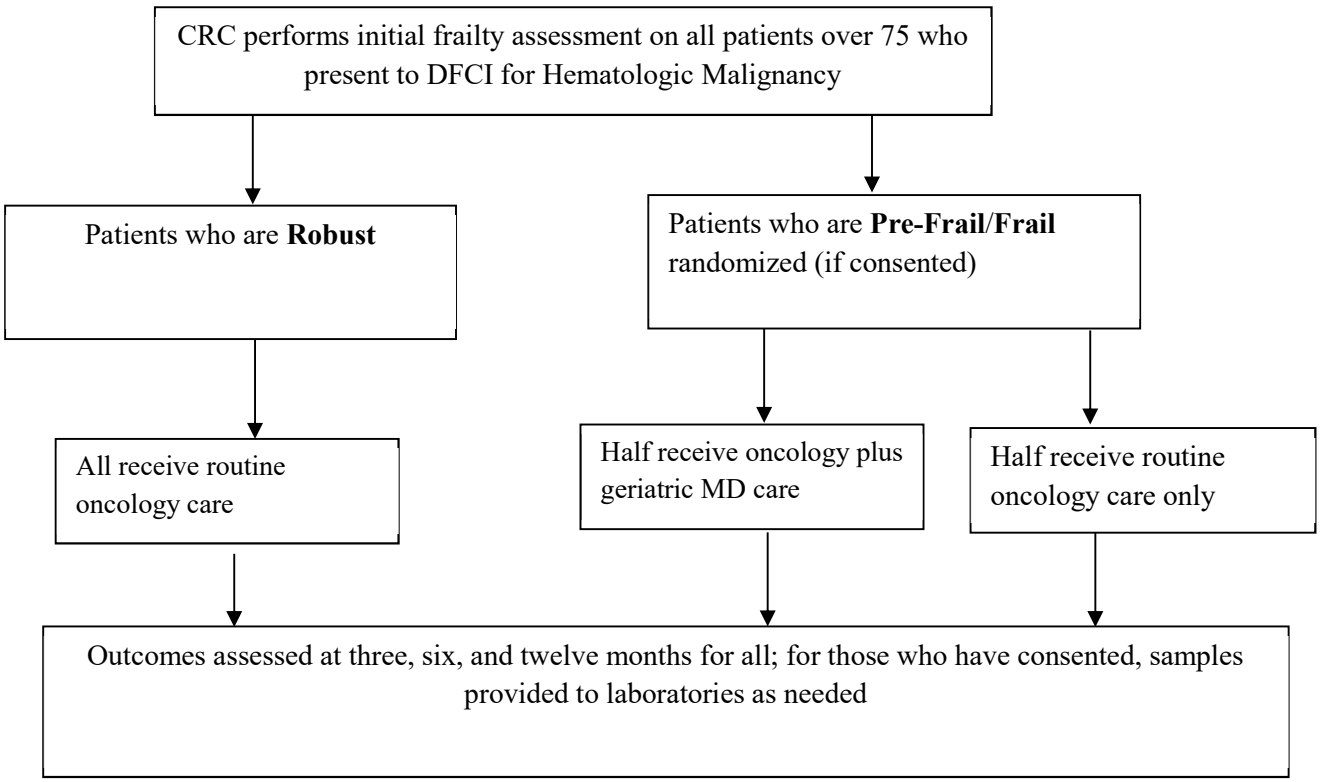
PROTOCOL SCHEMA:



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1.0 SUMMARY

We are interested in measuring the frailty of older blood cancer patients with precision, determining how much it contributes to prognosis compared with clinical disease-specific measures, and determining if co-management by a geriatrician embedded in the oncology clinic can improve outcomes. We thus propose to characterize the prognostic value of frailty as compared to clinical prognostic models for older patients with blood cancers, and, using a randomized design, determine if co-management of frail older adults with blood cancers by an embedded geriatrician reduces frailty and/or improves outcomes such as survival and non-scheduled hospital admissions.

2.0 BACKGROUND/RATIONALE

2.1 Overview

The Institute of Medicine (IOM) defines patient-centered treatment as "care that is respectful of and responsive to individual patient preferences, needs, and values."[1] Given the explosion in diagnostic and treatment options and the aging of the US population, this focus is arguably nowhere more important than in cancer care for the elderly. In their recent report**, "**Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis," the IOM made recommendations for older cancer patients, whose population is poised to double in less than two decades.[2] The report describes the complexity of caring for older adults with cancer, as they have multiple chronic conditions, decreased cognition, may need assistance in activities of daily living, and may be more vulnerable to treatment side effects. The biology of their cancers is also often different, as it may result from—or interact with—age-related somatic mutations not seen in younger patients. Recommendations for this coming "crisis" included using "evidence-based care parameters" as the basis for medical decisions. This seems a tall order, given that there are sparse data to inform care for this population.

Aging is the result of the accumulation of molecular and cellular damage over time, eventually leading to a loss of this physiological reserve across many organ systems. In turn, frailty describes a state in which physiologic reserve is depleted to the point that even small stressors can result in poor outcomes, including delirium, falls, disability and death.[3] Markers of frailty are very common in older patients with hematologic malignancy—over half have evidence of malnutrition, and over a third have impaired physical function.[4] Increased frailty in this population has been associated with increased chemotherapy-related toxicity, poor response to therapy, inability to complete planned course of therapy, and mortality.[5] Accordingly, the National Comprehensive Cancer Network recommends the incorporation of frailty assessment into the routine care of older cancer patients.[6]

Frailty is a dynamic process that can worsen or improve over time. For example, elderly cancer patients who undergo inpatient geriatric assessment and management have been shown to become less frail, more likely to return home, and less likely to have cognitive or functional decline.[7] Inpatient geriatric co-management has also been shown to substantially improve mood, social function and pain management post-discharge.[8] A systematic review of geriatric evaluation and management of older adults with blood cancers found that non- oncologic interventions are implemented by geriatricians in over 70% of patients, most often targeting nutrition, mood, physical function, polypharmacy, and social function.[4]

While there are limited studies regarding geriatric co-management in the outpatient hematology setting, and no randomized controlled trials to determine the best model of

delivering such care, observational research is instructive. Elderly AML is an excellent example: our own work has shown that markers of frailty are independent prognostic factors for death in models that included cytogenetic risk group, even for those patients with good baseline performance status (ECOG 0-1).[9] Given this context, we are interested in measuring the frailty of older adults with blood cancers with precision, determining how much it contributes to prognosis compared with clinical disease-specific measures and molecular markers, and determining if co-management by a geriatrician embedded in the oncology clinic can decrease frailty and improve disease-related outcomes.

Indeed, we have begun to see the increased burden of caring for elderly patients in hematologic oncology at Dana-Farber. During the period March 2013 to February 2014, for patients 75 and older, we had 3429 clinical visits in lymphoma (674 unique patients), 1704 for leukemia/related disorders (318 unique patients), and 3,245 for multiple myeloma (516 unique patients). Our older patient volume reflects an outstanding opportunity to both improve our care delivery and research the impact of frailty on disease outcomes. We wish to launch a research program to engage these patients in formal geriatric assessment and management, with the aim of addressing this important clinical and data gap.

2.2 Frailty Assessment

There are many frailty models, but two of the most commonly used models are the phenotype model and the cumulative deficit model.[10] The phenotype model is a categorical model that uses 5 separate variables to identify frailty. The variables are interrelated and are indicative of decreased physiologic reserve and resistance to stressors, two conditions that constitute the clinical definition of frailty.[3] The phenotype model is also popular because of its clinical reproducibility.[11] The cumulative deficit model is a continuous model of frailty that uses assessment of a large index of symptoms to determine frailty status,[10,12] with a higher number of symptoms leading to a greater likelihood of being frail.[10,13] The cumulative deficit model is popular because it can evaluate impairments in many biological systems, is graded, and is conceptually simple.[13]

Rockwood and Mitnitski created a standard cumulative deficit approach with their Comprehensive Geriatric Assessment (CGA), with approximately 40 variables, some of which are self-reported (e.g. “how would you rate your health?”), others are ascertained by tests such as the Montreal Cognitive Assessment (MoCA)[14], and others are determined by clinical evaluation (e.g. high blood pressure).[15] The efficacy of this model was examined by Searle et al. in a 2008 study, which analyzed a group of 754 community dwelling elderly people who were assessed and then longitudinally followed for outcomes. [12] The study found that the CGA was a significant predictor of mortality.

Sheppard et al. examined a cohort of 1,288 older women with breast cancer in order to validate use of this frailty index in a cancer population, aiming to assess its utility in predicting non-initiation or discontinuation of adjuvant hormonal therapy.[16] The investigators used a 35-item index adapted from the Searle approach. The index included self-reported items relating to limitations in basic and instrumental activities of daily living, sensory deficits, functioning, and the pre-diagnosis of comorbidity. They did not include measures of cognitive impairment, because women with cognitive impairment were excluded.

After calculating frailty scores on the 0-1 scale, cut-points of 0-0.2 for “robust”, 0.2-0.35 for “pre-frail”, and 0.35-1.0 for “Frail” were used. The study found that both frailty and pre-

frailty were significantly related to non-initiation of therapy. Although a trend was cited for frailty or pre-frailty and discontinuation of therapy, after considering covariates, no significant relationship was demonstrated. These data suggest that the frailest women never initiated therapy, which may explain why a significant relationship between frailty and discontinuation was not observed.[16] Sheppard concluded that although the results for frailty were suggestive, they should be confirmed in other studies of cancer populations. We will aim to apply this cumulative deficit assessment technique to DFCI's older hematologic oncology population.

The phenotype approach takes into account 5 factors that indicate frailty, including unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. After evaluation, people with 3 or more of the factors are categorized as "frail", people with 1 or 2 factors are "pre-frail" and people with no factors are "robust".[10] In a longitudinal study of community dwelling men and women aged 65 and older, Fried and associates found that people who were initially categorized as frail based on the phenotype model had more adverse outcomes at 3 and 5 year follow ups compared to people who were categorized as robust. Those who were found to be pre-frail at baseline exhibited outcome measures that fell intermediate between the other two groups.[3] Our study will look to expand upon these results and validate the phenotype approach, in addition to the cumulative deficit approach above.

2.3 Potential Benefits

The clinical and research program we propose will involve formal geriatric assessment and management of older patients with hematologic malignancies. This will likely be of direct benefit to patients as geriatric assessment has been shown to improve functional status, decrease hospitalization, and even lengthen life in non-cancer populations. In addition, by providing these services in the setting of a randomized controlled trial, we will be able to assess the efficacy of geriatric co-management and determine which components are most valuable to improving patient outcomes. Our study will help to further validate frailty assessment as a tool for the evaluation of geriatric cancer patients. Finally, this project will generate a comprehensive database of clinical and disease-specific factors that will allow us to build models to predict prognosis and toxicity and provide pathologic samples of older patients with hematologic cancers for study in the laboratory. These data in turn will ultimately be used to individualize cancer therapy for older patients with hematologic cancers.

3.0 OBJECTIVES/STUDY AIMS

The goal of this study is to establish a research program – the Older Adult Hematologic Malignancy (OHM) program – that will address important gaps in data about how best to care for older adults with hematologic malignancies. It is clear that markers of frailty are important predictors of tolerance of therapy and survival, but few studies have assessed their value in this population. Geriatric assessment and co-management are associated with improvements in quality of life, resource utilization and survival, but have not been tested scientifically in hematologic malignancies. We therefore propose the following specific aims:

3.1 Specific Aim 1

Characterize the prognostic value of frailty as compared to clinical prognostic models for older patients with blood cancers. We will perform a combined frailty

assessment in patients 75 and older who present to DFCI with a new diagnosis of MDS or a hematologic malignancy. Patients will be categorized as robust, pre-frail or frail based on their frailty score. We will then determine how the presence or absence of frailty predicts important outcomes such as treatment, resource utilization and mortality. In a subset of patient who specifically agree, frailty will be re-assessed at subsequent visits.

Hypothesis: Frailty will predict survival for those older patients with low-risk disease on molecular markers/disease-based risk systems, but be trumped by these for patients with high-risk disease.

3.2 Specific Aim 2

Determine if co-management of frail and pre-frail older adults with blood cancers by an embedded geriatrician improves outcomes. Patients who score as pre-frail or frail will be randomized to geriatric assessment and co-management with a geriatrician or usual care. They will be followed for disease-specific outcomes, with the primary outcome being overall survival at 1 year.

Hypothesis: For those assessed to be frail with rigorous measurement, co-management by an embedded geriatrician will improve overall survival at one year.

4.0 ELIGIBILITY

All patients aged 75 and older who present for an initial consultation at the DFCI for MDS or a hematologic malignancy (transplantation consultation excluded). For Specific Aim 2, insurance information will be reviewed to ensure geriatric referral is covered for all potential participants. This step will allow us to avoid a situation arising wherein a participant is randomized to geriatric co-management, yet their insurance does not cover geriatrician visits. As baseline geriatric assessment by our research assistant and later randomization to co-management by a geriatrician are currently precious resources, in practicality, to be eligible, patients will have to present on one of the three days per week that geriatric assessments are available, and be willing to be seen for geriatric co-management on one of the two geriatrician clinic days.

5.0 STUDY DESIGN and PROCEDURES

5.1 Patient Selection and Recruitment

All eligible patients will be given an appointment with our clinical research coordinator before their first meeting with their hematologist to discuss the study. This CRC will have been trained in frailty assessment by Dr. Driver and will be responsible for obtaining informed consent and completing the baseline frailty assessment for patients who consent. Importantly, patients will be able to consent to the baseline assessment, a potential follow-up assessment at a future visit, and/or allowing collection of extra samples for the laboratory. Categorical frailty status (robust versus frail/pre-frail) will be emailed to clinicians.

For Specific Aim 2 (now closed to enrollment), patients will be allowed to see a geriatrician outside of the trial design if they ask for this or if their physician requests it. We acknowledge that this may somewhat affect our randomized design, however, we feel that it is important to offer this service. Frail or pre-frail patients who were not randomized to geriatric

co-management but who see a geriatrician anyway will first be analyzed in an intent-to-treat manner and then excluded from a secondary analysis to assess if this event affects overall findings.

As above, frail, pre-frail and robust patients will undergo additional prospective evaluation to assess for study outcomes: for Specific Aim 1 we will compare frail and pre-frail patients who did not see a geriatrician to robust patients, and for Specific Aim 2, we will compare frail and pre-frail patients who saw a geriatrician to those who did not (see schema).

For all patients who go on to see a geriatrician, whether inside or outside of the trial design, continued follow-up (i.e. past the initial comprehensive geriatric assessment) will be determined by discussion between the geriatrician, the patient, and the patient's DFCI oncologist. As long as this resource remains available, patients will be able to follow-up with our geriatricians as long as they continue to receive their care at DFCI.

5.2 Registration Procedures

*5.2.*1 General Guidelines for DF/HCC and DF/PCC Institutions

For those who enter the randomized portion of the study, we will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

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

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

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist. These are that the patient be aged 75 and older, present for consultation at the DFCI for MDS or a hematologic malignancy, and be assessed as frail or pre-frail.
- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.
- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.
- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

5.3 Frailty Measures

We will use a combination of validated frailty assessment tools which are listed in Appendix A and summarized below in Tables 1 and 2. Using both the phenotype and cumulative deficit models (see above) is beneficial to provide more validity for a frailty assessment, and

cross validity between the two models has been established.[11,17] At current, there is still some debate as to the true clinical definition of frailty, and different studies have used different approaches to assess the frailty.[11] Using both models will allow for a more rigorous evaluation.

Table 1: Summary of cumulative deficit domains

Domain	Administration	Variable type	Cut-point
Functional Status in ADLs[12,18]	Patient questionnaire #1-14[12,19,20]	Binary	See Appendix A
Overall self assessment of health and performance Status[12,21]	Patient Questionnaire #15-20, verified by physician report	Continuous	See Appendix A
***Weight loss[3,11,12]**	Patient questionnaire #21	Binary	See Appendix A
***Self-reported exhaustion[3,11,12]**	Patient questionnaire #22-23	Continuous	See Appendix A
Psychological Status[12,18]	Patient questionnaire #24-26	Continuous	See Appendix A
Comorbidity[12,18-20]	Medical Record Review	Continuous	See Appendix A
***Physical Function and BMI[3,11,12]**	Grip strength, gait speed, and BMI recorded by research assistant	continuous	See Appendix A
Cognition[18]	MoCA[14] delayed recall and Clock in the Box[22] tests administered by research assistant	continuous[12]	See Appendix A

*Also included in phenotype assessment

Table 2: Summary of phenotype questions

Domain:	Measure:	Administration:	Results:

Weight Loss	In last year, weight has decreased by greater than or equal to 10 lbs or 5% of body weight[3,11]	Patient questionnaire #21 and medical record review by research assistant	Positive: Patient has lost 10 lbs or more in last year [3,11] Negative: Patient has not lost 10 lbs or more in last year[3,11]
Self-reported Exhaustion	Two questions from the CES-D Scale[23] about exhaustion	Patient questionnaire #22-23	Positive: Patient answers: "most of the time" for either question Negative: Patient answers: "some of the time" or "rarely" for both questions[3]
Energy Expenditure	Ability to walk[11]	Patient questionnaire #4 and ability to complete gait speed test at time of assessment	Positive: Needing assistance with walking or being unable to walk Negative: No assistance needed for walking[11]
Gait speed	NIH 4 meter gait speed test[24,25]	Administered by research assistant	Positive: Rapid gait speed less than or equal to cut-points provided by Gill et al.[26] Negative: Rapid gait speed greater than cut-points provided by Gill et al.[26]
Grip strength	Jamar Hand Dynamometer (Sammons Preston Roylan, Bolingbrook, IL) grip strength test[26]	Administered by research assistant	Positive: Average strength less than or equal to the cut-points provided by Fried et al.[3] Negative: Average strength greater than the cut-points provided by Fried et al.[3]

We will calculate two scores for frailty; one based on the cumulative deficit model and the other on the phenotype model. If patient's score as frail or pre-frail by either method they will be eligible for evaluation by a geriatrician.

For the Cumulative deficit score (table 1), the cumulative total of deficits is determined by adding all of the deficits that are present (deficit present = 1, deficit absent = 0, and for some variables, partial deficit = 0.25, 0.5, or 0.75) and dividing the result by the total number of items in the index. This study will use a frailty index comprising of 42 items (see appendix A). Of note, up to 92 symptoms can be assessed, although as few as 30 items can be used without loss of predictive validity.[18,20] Furthermore, the actual composition of the index is not crucial. As long as a sufficient number of variables are used, the variables can be selected at random and still yield comparable results.[27] After calculating a total frailty score on the 0-1 scale, cut-points of 0-0.2 for "robust", 0.2-0.35 for "pre-frail", and 0.35-1.0 for "frail" will be used to categorize patients, as was done in the Sheppard study.[16]

For the Phenotype score (table 2), the 5 phenotype variables will be assessed by obtaining information both from the patient questionnaire and from physical tests administered by the

research assistant. After evaluation, people positive for 3 or more of the factors are categorized as "frail", people with 1 or 2 factors are "pre-frail" and people with no factors are "robust".[10] Of note, all 5 of the phenotype measures are also included in the cumulative deficit assessment.

5.4 Data Collection Procedures

Patients will be approached by the research assistant prior to their scheduled appointment with a DFCI oncologist. The research assistant will consent the patients and then commence the frailty assessment. First, a 26 item self-report questionnaire (see appendix B) will be filled out by the patient. Next, the research assistant will administer the delayed recall section of the Montreal Cognitive Assessment (MoCA), clock-in-the-box test, grip strength test, and gait speed test. That will end the in-person frailty assessment. At baseline, the research assistant will perform a medical record review to obtain comorbidity information and body mass index. A follow up medical record review will be completed at one year from enrollment in order to obtain the outcome data listed in Table 3, which are all secondary outcomes of interest. There will also be general periodic assessments for overall survival.

Table 3: Summary of outcomes

Outcome:	Timeline for assessment:	Operationalization	Obtained from:
Survival*	6 months, 1 year	Overall survival	Patient medical record and outside records
Disease severity	Baseline	Disease Severity	Patient medical record and outside records
Treatment assignment	6 months	Supportive care only vs. chemotherapy vs. low dose chemotherapy vs. investigational treatment; any disease-modifying treatment versus not	Patient medical record and outside records
Hospitalizations	6 months	Number and length of hospitalizations since enrollment	Patient medical record and outside records
Emergency department visits	6 months	Number of ED visits	Patient medical record and outside records
Code status documentation	6 months	Code status entered into the medical record	Patient medical record
Continuation of care at DFCI	6 months	Number of visits and length of follow-up at DFCI; receipt of treatment at DFCI	Patient medical record
Δ Number of medications	Baseline to 3 months	Overall number of medications = number of cancer meds + number of non cancer meds	Patient medical record
Δ Blood pressure	Baseline,6 months	Measured at each visit	Patient medical record
Content Analysis of Notes	6 months	Only patients randomized to geriatrician	Patient medical record

**primary outcome*

5.5 Laboratory Correlates

We have engaged Dr. Ebert, Dr. Lane, Dr. Ritz and Dr. Wu as active members of the OHM team. We are hopeful that our new infrastructure for the rapid identification and provision of samples to their labs (one of the CRC duties, see below) will result in acceleration of current efforts at characterizing hematopoietic events specific to the elderly with blood cancers. Each week, we will provide them with de-identified list of patients -- gender, age and malignancy type -- who have consented to extra samples and are coming in for blood draw and/or marrow. These samples will serve as a source of controls for ongoing studies focusing on how age-related

changes in hematopoietic progenitor subsets, changes in the bone marrow, and in circulating levels of cytokines observed in healthy older individuals may evolve into frank cancer. They will also serve as a source of overt cancer samples to compare to candidate markers from the new pre-cursor clinic, which is expected to contain many elderly patients.

More specifically, we have identified a potential biomarker of interest, $p16^{INK4a}$, a tumor suppressor protein in the peripheral blood as an objective measure to elucidate the association between frailty and disease genetics.[28] Patients who have consented to providing additional samples from blood tests and return to Dana-Farber will have their $p16^{INK4a}$ levels measured. The samples will be collected from DFCI Lab Services and then processed by personnel in the Lane lab. All forms of patient identification associated with the sample will be removed and coded only with the corresponding OHM patient identification number. If the patient's frailty assessment is more than two weeks old, we will also approach the patient to conduct a second assessment.

We will measure $p16^{INK4a}$ expression from peripheral blood T-cells isolated by magnetic bead separation, where CD3+ and CD3- fractions will be isolated, cell pellets flash frozen, and additional aliquots viably cryopreserved in 10% DMSO. Total RNA will be isolated from CD3+ T cell pellets and $p16^{INK4a}$ expression will be measured using a validated Nanostring assay developed by the Burd lab at Ohio State University. As the characterization of $p16^{INK4a}$ is only available at OSU, we will be procuring the services of Dr. Burd's lab as an external resource to analyze $p16^{INK4a}$ levels in our samples. To facilitate preliminary analyses and to be able to combine with existing $p16^{INK4a}$ normative data at OSU, Dr. Burd's lab will be sent limited clinical data for each sample: age, gender, malignancy, frailty status, and ECOG score. Of note, these data will only be linked to participants via study ID; Dr. Burd's lab will not be sent participants' names, medical record numbers, dates of birth, or any other identifying data. Both the study data and the resulting analyses will be sent electronically as secure and encrypted files.

Additionally, stored cell pellets and cryopreserved cells will be used for orthogonal validation experiments in the Lane lab, including additional sorting of viable cells (e.g., if other cell types, or subpopulations within CD3+ T cells are suggested to be relevant based on our pilot studies or others' data). Individual patient samples in the Lane lab will be destroyed one year after enrollment of the last participant of the study.

The integration of molecular diagnostics could lead to a new paradigm at the population level. These data may allow some (robust) older patients with blood cancers appropriately receive full-dose treatment despite their advanced age, and others (frail) are protected from unnecessary morbidity arising from the same. It also addresses issues relevant to the unequal burden of cancer and outcomes in diverse populations, as the frail elderly have both a higher incidence of cancer and also experience generally less favorable outcomes.

6.0 ANALYTIC CONSIDERATIONS

6.1 Specific Aim 1

We will first perform descriptive analyses of covariates of frailty/pre-frailty in our population, including age, gender, race-ethnicity, and disease type. Means and proportions will be used to describe patient characteristics, individual and summary frailty responses, baseline clinical data, and treatment assignment. We will identify variables that are associated with the outcomes of interest using Kaplan-Meier curves and log-rank tests. Given limited numbers of patients and other study resources, we will plan to combine the frail and pre-frail groups in our

analyses for Aim 1 (frail/pre-frail versus robust), but if power allows, we will also compare outcomes for all three groups (frail versus pre-frail versus robust).We will use the tests above for univariate analyses to determine whether any of the relevant geriatric domains, socio-demographic factors, or clinical data are associated with choice of treatment, length of time in the hospital and survival. We will also perform univariable and multivariable analyses to determine if frailty interacts with other patient characteristics to influence outcomes. We will also conduct analyses specific to disease clinics at DFCI (MDS/leukemia versus lymphoma versus myeloma). We will consider a p value < 0.05 to be significant, and all analyses will be carried out using SAS v.9.

6.2 Specific Aim 2

For frail patients, pre-frail patients and the combined cohort, we will create multivariable models to assess the impact of geriatric co-management on the outcomes listed in Table 3, controlling for age, gender, race-ethnicity, and disease type. We will consider a p value < 0.05 to be significant, and all analyses will be carried out using SAS v.9. Of note, we again plan to combine the frail and pre-frail groups in our analysis given limited resources and lack of current data as to whether or not geriatric intervention is more helpful in one of these groups; if power allows (see below), we will also adjust for frail versus pre-frail status.

6.3 Power Considerations

Power analysis is based on Specific Aim 2, as the patients enrolled therein will be a subset of the patients from Specific Aim 1. The study is powered to detect a difference in the one-year overall survival rate (i.e., the primary endpoint) between the two groups in Specific Aim 2: those patients who see a geriatrician (Group 2) and those who do not (Group 1). Based on prior observational data, overall survival in Group 1 is expected to be 68% at one year (this is based on the one-year OS of a sample of 114 MDS patients followed at DFCI from 2006 to 2012). We expect the one-year overall survival rate in Group 2 (the intervention group) to be 85%, which corresponds a 25% of improvement over Group 1. A total sample size of 160 (107 Group 1; 53 Group 2) would achieve 80% power to detect this difference, at 0.05 one-sided type I error level.

Indeed, the number of patients seen in the OHM program will be limited by the resources of the CRC and the geriatricians. In one year, given current numbers, we would expect 600 unique myeloma, lymphoma and AML/MDS patients over aged 75 (see above) to present at DFCI. We will be aiming to undertake baseline assessments for all new patients appearing on four calendar days each week. We originally hoped to have 540 potential patients for Specific Aim 1. As of December 18, 2017, 494 patients out of the 570 patients approached (87%) have agreed to Specific Aim 1. Given our line of success with enrolling patients since February 3, 2015, and after discussions with our clinicians, we hope to recruit three times the number of patients originally planned for this aim in order to conduct disease-specific analyses. We hope to have 1,620 potential patients for Specific Aim 1 so we may stratify analyses by our three disease-specific clinics at DFCI (MDS/leukemia, lymphoma, and myeloma).

If 216 (60%) of the 540 patients, originally planned for accrual, are ultimately assessed by the CRC, and 25% found to be frail or pre-frail continue to receive care at DFCI, and agree to the RCT, this leaves 54 to be randomized to geriatric co-management vs. routine oncology care (27 in each group) per year. Our hope is to reach a sample size of 160 patients (107 Group 1; 53 Group 2) for Specific Aim 2 in three years, but we will extend the study until we achieve this

enrollment. Of note, we have expanded our geriatrician clinics to two sessions per week to accommodate this increased patient load.

6.4 Randomization Procedures

Randomization will be stratified by general disease type (myeloma versus lymphoma versus MDS/AML). Specific procedures will include permutation block randomization in blocks of four and six to avoid predictability of intervention groups.

7.0 REGULATORY REQUIREMENTS

7.1 Informed Consent

Informed consent will be required for all patients in the study. Patients will be able to consent to the baseline assessment, a potential follow-up assessment at a future visit, and/or allowing collection of extra samples for the laboratory.

7.2 Patient Confidentiality

Subjects will be identified by their initials and study ID number only. All sensitive electronic information will be kept in a database on a secure server and will be accessed via a Partners desktop computer within DFCI or an encrypted and password protected Partners laptop. Data transfer will occur via encrypted thumb drive. In addition, the computers to be used in this project are stored in secure offices and are accessible only to authorized personnel. All sensitive paper information will be locked in a file cabinet in the principal investigator's office. All study personnel will undergo data security and confidentiality training. All data will be destroyed one year after relevant publications.

7.3 Potential Benefits of the Proposed Research

Patients may or may not benefit from this study. However, the benefit to society in this study is substantial. Discoveries made from this data will be useful to scientists, practicing physicians and individual patients. Specifically, as geriatric assessment and management have been shown to improve functional status, decrease hospitalization, and even lengthen life in non-cancer settings, we hope that our work will eventually create a more accurate prognostic model and patient-centered approach for older patients with blood cancers. The data we generate from our analysis will serve as pilot data for larger and grantable projects. In addition, we are hopeful that the creation of an infrastructure for the rapid identification and dissemination of samples to our wet lab collaborators will result in improving ongoing efforts at defining the important molecular mechanisms of hematologic cancers in the elderly, a vital future source of patient-centered care.

7.4 Importance of the Knowledge to be Gained

This study will generate valuable information about the treatment and outcomes of older patients with hematologic malignancies. This in turn will lead to improvements in the assessment and clinical care of these patients. The risk-benefit ratio is highly favorable given the potentially large societal benefits and essentially negligible risk to the participants.

8.0 PROJECT TIMELINE

January 2015	Obtain OHRS approval
February 2015	Begin baseline geriatric assessments and randomization
August 2015	Interim analysis for Specific Aim 1
May 2018	Finish enrollment for Specific Aim 2
June 2018 to August 2019	Continuing enrolling participants to Specific Aim 1; Interim analyses for Specific Aim 1; Analysis and abstract write-up for Specific Aim 2
September 2019 to January 2020	Final manuscript for Specific Aim 2
February 2020 to January 2024	Continuing enrolling participants to Specific Aim 1; Interim analyses for Specific Aim 1; Continue follow-up for outcomes.
January 2024 to January 2025	Specific Aim 1 analysis; Final manuscript for Specific Aim 1

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Appendix A: Frailty Scoring Values

Cumulative Deficit Model (CDM) Variable Index and Scoring

Obtainment		Measured Variable	CDM Scoring (scaled 0-1)
Patient questionnaire	1	Bathing	With some help or completely unable=1; Without help=0
	2	Dressing	
	3	Getting in/out of chair	
	4	*Walking around house	
	5	Eating	
	6	Grooming	
	7	Using Toilet	
	8	Getting up/down Stairs	
	9	Lifting 10 lbs	
	10	Shopping	
	11	Doing housework	
	12	Meal preparations	
	13	Taking medication	
	14	Handling finances	
	15	Walk outside	<3 days=1; ≤ 3 days=0
	16	Self-report ECOG PS	3-4=1; 1-2=0.5; 0=0
	17	Self rating of health	Poor=1; Fair=0.75; Good=0.5; V. Good=0.25; Excellent=0
	18	How health has changed in last year	Worse=1; Better/Same=0
	19	Stayed in bed at least half the day due to health (in last month)	Yes=1; No=0
	20	Cut down on usual activity (in last month)	
	21	*Lost more than 10 lbs in last year	
	22	*Feel Everything is an Effort	Most of time=1; Some time=0.5; Rarely=0
	23	*Have Trouble getting going	
	24	Feel Depressed	
	25	Feel Lonely	
	26	Feel Happy	Most of time=0, Some time=0.5, Rarely=1
Patient medical record	27	High blood pressure	Yes=1; Suspect=0.5; No=0
	28	Heart attack	
	29	CHF	
	30	Stroke	
	31	Cancer	
	32	Diabetes	
	33	Arthritis	
	34	Chronic Lung Disease	
	35	BMI	See Tables below for cut points
Assessed by research staff	36	*Grip strength	
	37	*Usual pace walk speed	

	38	*Rapid pace walk speed	
	39	Montreal Cog. Assessment 5 word delayed recall	
	40	Clock-in-the-box test	
	41	Ability to explain presentation to DFCI	With help or unable=1; Without help=0
	42	Ability to fill out the questionnaire	

* Also used in calculation of Phenotype Frailty Score

Physical variable cut-points[12]

Variable	Deficit for Men	Deficit for Women	Source of Cut point
Body Mass Index (BMI)	<18.5, ≥ 30 as a deficit. 25-<30 as a 'half deficit'	<18.5, ≥ 30 as a deficit. 25-<30 as a 'half deficit'	Published [29]
Grip Strength (GS in kg)	For BMI ≤ 24, GS ≤ 29 For BMI 24.1–28, GS ≤ 30 For BMI >28, GS ≤ 32	For BMI ≤ 23, GS ≤ 17 For BMI 23.1–26, GS ≤ 17.3 For BMI 26.1–29, GS ≤ 18 For BMI>29, GS ≤ 21	Published [3,26]
Rapid pace Walk	<0.61 m/s (6.56 sec)	<0.61 m/s (6.56 sec)	Published [26]
Usual pace Walk	<0.38 m/s (10.50 sec)	<0.38 m/s (10.50 sec)	Published [12]

MoCA 5 word delayed recall normative data and cut-points[14]

Memory	Normal Control		Mild Cognitive Impairment		Alzheimer's Disease	
	AVG	SD	AVG	SD	AVG	SD
	3.73	1.27	1.17	1.47	0.52	1.03

Words Recalled Successfully	5	4	3	2	1	0
Corresponding CDM Score	0	0.25	0.5	0.75	1	1

Clock-in-the-box normative data for age and education and cut-points[22]

Age (y)	Education			
	Less than High School (SD)	High School (SD)	College (SD)	Graduate School (SD)
75-79	5.1 (1.9)	6.3 (1.6)	6.4 (1.3)	6.6 (1.4)
80-84	4.6 (1.9)	5.8 (1.5)	5.9 (1.6)	6.7 (1.2)
≥85	4.9 (1.3)	5.4 (1.3)	5.8 (1.7)	6.5 (1.5)

CIB Score	8	7	6	5	0-4
Corresponding CDM Score	0	0.25	0.5	0.75	1

Phenotype Model Variable Index

	Index Item*	Measured Variable	Scoring
1	21	Weight loss	Yes=1, No=0
2	22,23	Self-Reported Exhaustion	Most of the time (for either)=1, some or rarely (for both)=0
3	4	Energy Expenditure	Some assistance or completely unable=1, without assistance=0
4	37,38	Gait Speed (usual and rapid pace)	Slower than cut-point=1 (for either), faster than cut-point=0
5	36	Grip Strength	Weaker than cut-point=1 (for strongest measurement), stronger than cut-point=0

*Numbers correspond to item number in Cumulative Deficit Variable Index (Appendix A).

Appendix B: Patient Questionnaire

The following items (1-14) are about activities you might do during a typical day. Are you able to do these activities- Without help? With Some Help? or Completely Unable?

(Please Circle One Number on Each Line)

	Without help	With Some Help	Completely Unable
1. Taking a bath or shower	[1]	[2]	[3]
2. Getting Dressed	[1]	[2]	[3]
3. Getting in/out of a chair	[1]	[2]	[3]
4. Walking around the house	[1]	[2]	[3]
5. Eating	[1]	[2]	[3]
6. Grooming (personal hygiene)	[1]	[2]	[3]
7. Using the toilet	[1]	[2]	[3]
8. Going up/down stairs	[1]	[2]	[3]
9. Lifting 10 lbs	[1]	[2]	[3]
10. Shopping	[1]	[2]	[3]
11. Doing housework	[1]	[2]	[3]
12. Preparing meals	[1]	[2]	[3]
13. Taking medication	[1]	[2]	[3]
14. Handling your own money	[1]	[2]	[3]

15. During the last week, on how many days did you walk outside? (circle one)

0 1 2 3 4 5 6 7

16. Which option below describes your level of physical activity **over the past week?** (mark one)

- ☐ Fully active, able to carry on all usual activities without restriction

- ☐ Restricted in strenuous activity; can walk; able to carry out light housework
- ☐ Can walk and care for self; up more than 1/2 day
- ☐ Need some help taking care of self; spend more than 1/2 day in bed or chair
- ☐ Cannot take care of self at all and spend all of my time in bed or chair

17. Overall, how would you rate your health? (circle one)

Excellent Very good Good Fair Poor

18. How would you say your health has changed in the last year? (mark one)

☐ Worse ☐ Same ☐ Better

19. In the last month, have you ever stayed in bed at least half of the day due to your health?

☐ Yes ☐ No

20. In the last month, have you cut down on your usual activity due to your health?

☐ Yes ☐ No

21. Have you lost more than 10 lbs unintentionally in the last year?

☐ Yes ☐ No

22. How often do you feel that everything is an effort?

☐ Most of the time ☐ Some of the time ☐ Rarely

23. How often do you feel that you have trouble getting going?

☐ Most of the time ☐ Some of the time ☐ Rarely

24. How often do you feel depressed?

☐ Most of the time ☐ Some of the time ☐ Rarely

25. How often do you feel lonely?

☐ Most of the time ☐ Some of the time ☐ Rarely

26. How often do you feel happy?

☐ Most of the time ☐ Some of the time ☐ Rarely

Supplemental Figure 1: Survey Instrument

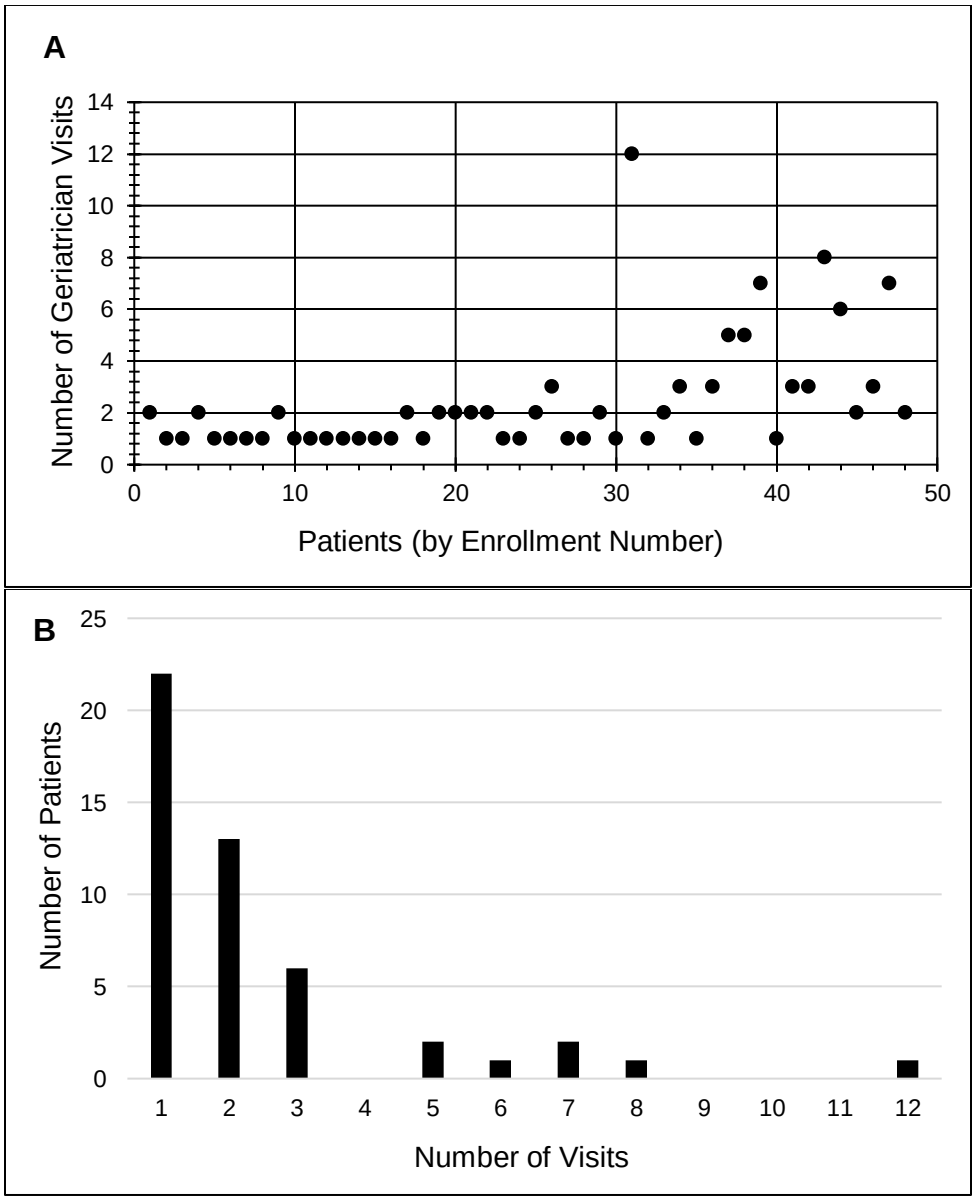
Q2. On a scale of 1 (least useful) to 5 (most useful), how would you rate the usefulness of geriatric services in the following areas?

	1-Least Useful	2	3	4	5-Most Useful
Diagnosing frailty	○	○	○	○	○
Evaluating cognition	○	○	○	○	○
Informing treatment decisions	○	○	○	○	○
Tailoring end-of-life care	○	○	○	○	○
Connecting patients to resources	○	○	○	○	○
Managing non-oncologic comorbidities	○	○	○	○	○

Q3. On a scale of 1 (least helpful) to 5 (most helpful), how helpful are geriatric services for your patients in managing the following?

	1-Least Helpful	2	3	4	5-Most Helpful
Depression	○	○	○	○	○
Functional Status	○	○	○	○	○
Falls / Fall Risks	○	○	○	○	○
Insomnia	○	○	○	○	○
Mood Disorders	○	○	○	○	○
Nutrition	○	○	○	○	○
Pain	○	○	○	○	○

Supplemental Figure 2: Number of geriatrician visits in intervention group who completed at least one consult visit with geriatrician (n = 48). **A:** Number of geriatrician visits by enrollment order of participants. **B:** Number of patients by increasing number of visits.



Supplemental Table 1: Latest active treatment regimens within three months of initial consult

Treatment Regimen	All (n=160)	Standard Oncologic Care (n=100)	Geriatric Consultation + Standard Care (n=60)
Receipt of treatment prior to consult	61	32	29
Observation	47	34	13
Supportive[a]	13	8	5
Hospice	4	1	3
Lost to follow-up	1	1	0
Radiation only	2	2	0
Azacitidine	6	2	4
Bendamustine	1	1	0
Bortezomib (w/ or w/out dexamethasone)	4	3	1
Capecitabine	1	0	1
Carfilzomib, pomalidomide (w/ or w/out dexamethasone)	1	0	1
CHOP	1	1	0
Clinical trial drug (name undisclosed)	1	1	0
Cyclophosphamide, bortezomib (w/ or w/out dexamethasone)	4	3	1
Daratumumab (w/ or w/out dexamethasone)	3	2	1
Daratumumab, lenalidomide (w/ or w/out dexamethasone)	2	1	1
Daratumumab, pomalidomide (w/ dexamethasone)	1	1	0
Dasatinib (w/ or w/out dexamethasone)	2	1	1
Decitibine	3	2	1
Hydrea	2	0	2
Ixazomib, lenalidomide (w/ or w/out dexamethasone)	1	0	1
Ixazomib, pomalidomide (w/ or w/out dexamethasone)	1	1	0
Ixazomib, rituximab, dexamethasone	1	1	0
Ibrutinib	7	3	4
Imatinib	3	1	2
Lenalidomide (w/ or w/out dexamethasone)	8	5	3
Lenalidomide, bortezomib (w/ or w/out dexamethasone)	15	8	7
Methotrexate	1	0	1
Prednisone	1	1	0

R-CHOP	5	3	2
R-miniCHOP	2	1	1
R-EPOCH	1	1	0
R-GCVP	1	1	0
Rituximab	5	3	2
Rituximab, bendamustine	4	3	1
Ruxolitinib	1	0	1
Venetoclax	3	3	0
Vinblastine	1	1	0

[a]Supportive included erythropoietin agents, bone marrow stimulants, and/or blood transfusions. Abbreviations: CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin), prednisone; R-CHOP, rituximab-CHOP; R-miniCHOP, reduced dose CHOP; R-EPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate (oncovin); cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin); R-GCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone.

Supplemental Table 2: Full multivariable Cox proportional hazards regression model assessing effect of geriatric consultation on 1-year overall mortality. Separate model was run for per-protocol analysis.

One-year Overall Mortality	Hazard Ratio (95% CI)	P Value
Intent-to-treat vs control (N=160) adjusting for age, sex, disease aggressiveness and frailty		
Intent-to-treat vs control	0.93 (0.45 - 1.95)	0.85
Age	1.01 (0.93 - 1.09)	0.86
Sex (male vs female)	2.25 (0.96 - 5.28)	0.06
Aggressive disease	0.97 (0.46 - 2.01)	0.93
Pre-frail vs Frail	0.46 (0.21 - 0.99)	0.05
Per-protocol vs control (N=148) adjusting for age, sex, disease aggressiveness and frailty		
Per-protocol vs control	0.70 (0.30 - 1.66)	0.41
Age	1.01 (0.93 - 1.12)	0.75
Sex (male vs female)	2.84 (1.07 - 7.57)	0.04
Aggressive disease	0.89 (0.41 - 1.96)	0.78
Pre-frail vs Frail	0.44 (0.20 - 1.00)	0.05

Abbreviations: CI, confidence interval

Supplemental Table 3: Full multivariable weighted logistic regression model assessing effect of geriatric consultation on 1-year overall mortality. Separate model was run for per-protocol analysis.

One-year Overall Mortality	Odds Ratio (95% CI)	P Value
Intent-to-treat vs control (N=160) adjusting for age, sex, disease aggressiveness and frailty		
Intent-to-treat vs control	0.64 (0.16 - 2.62)	0.54
Age	0.93 (0.78 - 1.11)	0.45
Sex (male vs female)	1.58 (0.32 - 7.74)	0.57
Aggressive disease	0.57 (0.15 - 2.25)	0.43
Pre-frail vs Frail	0.53 (0.12 - 2.32)	0.40
Per-protocol vs control (N=148) adjusting for age, sex, disease aggressiveness and frailty		
Per-protocol vs control	0.47 (0.01 - 19.14)	0.69
Age	0.93 (0.79 - 1.09)	0.36
Sex (male vs female)	2.37 (0.11 - 48.87)	0.58
Aggressive disease	0.48 (0.11 - 2.12)	0.33
Pre-frail vs Frail	0.49 (0.11 - 2.25)	0.36

Abbreviations: CI, confidence interval