BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Composite Health Assessment Risk Model for Older Adults: Applying Pre-transplant Comorbidity, Geriatric Assessment, and Biomarkers to Predict Non-Relapse Mortality after Allogeneic Transplant (CHARM)

Version 3.0

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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute

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PROTOCOL SYNOPSIS

Composite Health Assessment Model for Older Adults: Applying Pre-transplant Comorbidity, Geriatric Assessment and Biomarkers to Predict Non-Relapse Mortality after Allogeneic Transplantation

Co-Principal Investigators:	Andrew Artz, MD, MS and Mohamed Sorror, MD, MSc
Study Design:	Prospective observational multicenter study of allogeneic Hematopoietic Stem Cell Transplantation (HCT) in recipients 60 years and older to assess important determinants of health status to be combined into a composite health risk model to improve risk assessment of non-relapse mortality (NRM). At baseline, standardized Geriatric Assessment (GA) tools incorporating subject reported data and bedside testing will be collected. HCT-Comorbidity Index (CI) scores will be assigned and C-reactive protein (CRP) and albumin will be measured locally. Serial measures at 3, 6, and 12 months for frailty, skilled facility admission, and quality of life (QOL) using PROMIS measures for physical function, depression and anxiety will be determined. Graft Versus Host Disease (GVHD) through one year, serious toxicities through day 100, cognitive status at day 100 and causes of death will be captured.
Primary Objective:	To determine the set of assessments and biomarkers that could together constitute a robust and valid composite health risk model for accurate personalized estimation of one year NRM.
Secondary Objectives:	To determine the association of the composite health risk-model with differences in overall survival, frailty, disability, skilled-facility admission, cognitive decline, QOL and acute and chronic GVHD over the first year after transplant and with one year survival and with serious organ toxicity through day 100.
Eligibility Criteria:	Subjects 60 years of age or older able to speak and read English, Spanish or Mandarin and eligible for first allogeneic transplantation based on institutional standards. Subjects must have a planned allogeneic transplantation for a hematologic malignancy. Any allogeneic graft source or donor type will be permitted. Subjects must provide informed consent.

Treatment Description:

The GA consists of a panel of subject reported data and a health care team administered assessment as follows: 5 component Physical Frailty Phenotype, falls, instrumental activities of daily living (IADL), PROMIS physical function, cognition (Montreal Cognitive Assessment/MoCA), depression (PROMIS QOL Depression), polypharmacy and nutrition. These tools will be administered within 21 days of the start of conditioning. The HCT-CI score will be collected through review of the records. CRP and albumin will be performed at the center within 14 days of conditioning. Re-evaluation will occur at 3, 6, 12 months after transplantation for QOL (PROMIS physical function, depression, anxiety), frailty phenotype, facility admission, and IADLs. Subjects with relapsed disease will remain on study.

Statistical Design:

The primary method for building the CHARM to predict NRM will be a multivariate Cox proportional hazards regression model for the cause-specific hazard of NRM. Proportional hazards assumptions will be assessed for each variable using graphical approaches and time-dependent covariates; if proportional hazards are violated, time-dependent covariates will be used. Variable selection will be done using a step-wise model building approach. A composite health risk score will be constructed from the final Cox model by summing the log hazard ratios for each of the relevant covariates to be included in the scoring system.

The model will be adjusted for donor type and HLA matching, donor/recipient CMV status and intensity of conditioning regimen.

Sample size calculation is based on the ratio of the number of NRM events divided by the number of potential (candidate) predictors. This ratio is known as events per variable or simply EPV. In this study design, we aimed for an EPV of 12. The NRM rate in our subject population is estimated at approximately 22%. There are 13 variables to be tested for inclusion in the model and an additional 3 variables for adjustment with a total of 16 variables. Per the equation: (N x 22%)/16= 12 EPV, we will need a sample size of 880 subjects.

For model validation, the 632+ bootstrap cross-validation method will be used to estimate the prediction error and explained variation using the approach by Schemper and Henderson.

	Secondary endpoints will be evaluated using cumulative incidence, Kaplan Meier estimates and regression models as appropriate.
Accrual Objective:	The study will target accrual of 880 patients undergoing allogeneic transplant for model development. We anticipate consenting and enrolling 1100 patients with a 20% drop-out rate prior to transplantation.
Accrual Period:	Estimated accrual period is 24 months.
Study Duration:	There will be one additional year for follow-up. Total study duration is about 36 months.

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CHAPTER 1

1 BACKGROUND AND RATIONALE

1.1 Summary of the Clinical Problem

Current demographic changes in the US population have resulted in an increasing number of older subjects presenting for treatment of oncologic diseases. This trend is likely to continue for the foreseeable future. Older subjects are more often to have comorbid conditions, which has resulted observed higher rates of morbidity and mortality complicating therapy choices in subjects of advanced chronologic age. Age and co-morbid changes also require individualized modifications to standard therapies to enhance tolerability and safety. A number of disparate fitness and frailty tools used in geriatric medicine have been applied to older and unfit subjects undergoing chemotherapy, yet there are no robust guidelines on how, in whom and when to apply these assessment tools.

Older adults are also disproportionately diagnosed with high-risk hematologic malignancies that are difficult to cure without the use of allogeneic hematopoietic cell transplantation (HCT). Several advances in recent years have enabled HCT to be applied to older and more comorbid adults. However, transplant-related toxicities and non-relapse mortality (NRM) remain particularly problematic in this population when analyzed as a congregate whole. At the same time, although increasing numbers of adults over the age of 60 years are undergoing HCT, many who may benefit are either not referred, or not receiving HCT, due to a wide perception that older age alone may be a disqualifying factor in transplantation. For example, Pidala published a physician survey which reflected patient age substantially influenced referral for allogeneic HCT. [1] Surprisingly, 21% considered age 60 years or less an upper age limit for referral and only 17% would refer a patient 70 years and older. The barriers for referral and/or utilization for HCT are complex including insurance status, patient health, access to a transplant center, disease control, donor availability, physician bias and/or patient perceptions.

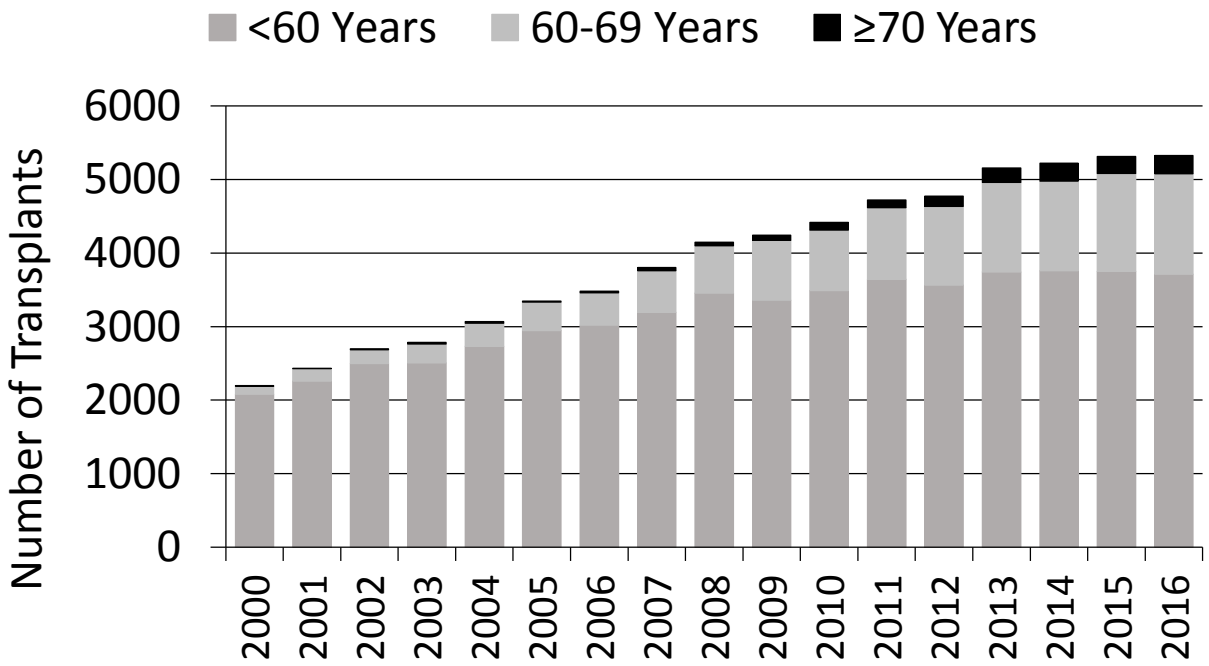
Given the limited number of trials specifically geared to illustrate the safety and utility of transplantation in older subjects, this knowledge deficit has led to a significant underutilization of potentially curative HCT therapy in this population. There is therefore a critical need to develop a validated, comprehensive risk assessment tool in older adults with hematologic malignancies considered for HCT, in order to identify subjects who will benefit most from transplantation. There are significant expected differences and potentiating factors for developing toxicities between standard and transplant therapies, even in reduced intensity transplantation. This means that simple extension and application of any of the array of geriatric oncology risk assessments used in standard intensity treatments will not reliably predict subjects who would be at risk for excess toxicity when undergoing allogeneic transplantation. This study aims to fill this knowledge gap through the development and validation of a comprehensive geriatric health assessment model for prognostication of NRM amongst older adults undergoing allogeneic HCT for hematologic malignancies. This need was identified at the 2014 BMT CTN State of the Science Symposia as a critical knowledge gap and represents a question that the BMT CTN is uniquely positioned to address.[2]

1.2 Allogeneic HCT in Older Adults

The majority of hematologic malignancies disproportionally affect older adults. For example, the median age of acute myeloid leukemia (AML) diagnosis in western countries is 67 to 70 years of age.[3] Standard of care, non-HCT therapies are rarely curative in older adults with AML, with long-term disease-free survival (DFS) of <15%.[4-5] Likewise, older age is a strong adverse factor for outcomes in other HCT-eligible hematologic malignancies such as myelofibrosis (MF) and acute lymphoblastic leukemia (ALL) due to refractory or recurrent disease.

The efficacy of allogeneic transplantation as curative therapy for hematologic malignancies and other disorders is well-established. The last decade has witnessed a rise in the use of allogeneic HCT for a variety of hematologic malignancies; however, the increased use of HCT has been most dramatic in adults over the age of 60 and even 70 years of age (Figure 1.2).

Figure 1.2: Trends in Allogeneic HCT by Subject Age, Center for International Blood and Marrow Transplant Research, 2000-2015



*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Several reports have depicted overall survival (OS) following HCT in older adult with AML and MDS. A review of 13 studies including 749 adults 60 years and older undergoing allogeneic HCT for AML found that overall survival (OS) at 1, 2 and 3 years was 58%, 45%, and 38%, respectively.[6] Devine et al. published results of a multi-institutional prospective study conducted jointly by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and the Cancer and Leukemia Group B (CALGB) in older adults using a low-intensity fludarabine-

busulfan-ATG regimen and matched related or unrelated donors for AML in first remission.[7] In this study of subjects 60 to 74 years of age, favorable 2 year OS of 48% was reported. Registry data for AML and Myelodysplastic Syndrome (MDS) subjects age 70 and older utilizing all donor sources and conditioning regimens showed 2 year survival of 38%.[8] Recent small series of haploidentical and umbilical cord graft studies in older AML subjects have described outcomes similar to matched donors among older adults, suggesting donor availability should not limit allografting in older subjects. [9-11] These results suggest that chronologic age alone should not be the sole determinant for allograft eligibility, and that other factors may better discriminate older subjects with better or worse outcomes. There have been several lines of inquiry into identifying the pre-transplant determinants of the traditional outcome measures for older subjects undergoing allogeneic transplantation.

1.3 Non-Relapse mortality following HCT in Older Adults

A central concern of utilizing the potent graft-versus-leukemia effects of allogeneic HCT in older adults is the risk of morbidity and mortality. Non-relapse mortality (NRM), or death without disease relapse, represents the most widely used objective measure of serious toxicity related to HCT.

We recently reviewed one-year outcomes for over 4000 subjects 60 years and older transplanted from 2012 to 2016 in centers participating in the BMT CTN. Despite the frequent use of reduced intensity (RIC) and non-myeloablative (NMA) conditioning regimens in these subjects, and the improvements of infectious disease and graft-versus-host disease (GVHD) management over the last decade, the one year NRM among these subjects treated at BMT CTN Core and Affiliate centers remained high at 19% and 25%, respectively. (*Verbal communication, W Saber, May 2018*). Further inspection of NRM amongst subjects treated at BMT CTN Core sites reveals that NRM increases with age (Table 5.1.2) (*Verbal communication, W Saber, May 2018*). EBMT investigators have shown similar results with those 70 years and older having greater risks of NRM relative to those under 70 years.[12] Likewise, CIBMTR data revealed that 2-year NRM amongst subjects 70 years and older undergoing HCT has remained stagnant at 33-34% over the past decade.[8]

1.4 Comorbidity and NRM following Allogeneic HCT

Although chronological age often factors into HCT prognostication, additional tools to more accurately measure physiologic age may be more discriminative for transplant outcomes. Older physiologic age as measured by function, comorbidity, biomarkers or health domains, tracks with shorter life expectancy, more toxicity, and biologic markers of senescence. [13]

The presence of comorbid health conditions (comorbidities) has long been recognized as bearing prognostic importance in oncology.[14] Although generic comorbidity scales exist for geriatric medicine and general oncology, a major advance in HCT risk assessment was achieved through the development and validation of the hematopoietic cell transplantation-comorbidity index (HCT-CI) by Sorror.[15] The HCT-CI has been extensively validated in both allogeneic and autologous HCT subjects.[16, 17] In a CIBMTR validation study including subjects of all ages receiving allogeneic transplants, one-year NRM rates were 17%, 21% and 26% for HCT-CI

scores of 0, 1 – 2 and 3, respectively (p <.001). [16] The HCT-CI also discriminates NRM in older adults, although the effect is most profound in those with very high comorbid burden (i.e., HCT-CI of 5 or more relative to HCT of 0; HR=1.77, 95% CI 1.50 – 2.10). Comorbidity and age were found to be additive in their prognostic effects on NRM and survival. [16, 18, 19]

1.5 Performance Status as a Predictor of NRM following Allogeneic HCT

Physician assessment of subject performance status (PS) is a widely used measure in HCT risk assessment and for eligibility. Low physician rated Karnofsky Performance Status (KPS) (e.g., <60-70%) often exclude patients from allogeneic transplant consideration and among older transplanted patients; KPS of 80% or less may have worse outcomes relative to 90% to 100%. [20] However, physician documented performance scales often do not adequately predict prognosis or NRM following HCT. This is likely in part due to the fact that the majority of older adults undergoing HCT have documented Karnofsky performance status of >80%. [20] Further, PS has ceiling effects as functional impairments are frequent among older patients with physician rated KPS of 90-100% undergoing HCT. [21]

1.6 Geriatric Assessment and Other Tools to Aid HCT Prognostication

1.6.1 Geriatric Assessment

Geriatric assessment (GA) represents the gold standard of health assessment characterization in older adults in community based medical settings. The GA is a multidisciplinary tool applied in Geriatrics and Geriatric Oncology covering multiple health domains, including comorbidity, function, nutrition, polypharmacy, psychologic health and social circumstances. [13] No standard set of assessments comprising a GA exist as instruments differ depending on the population, setting and time available for testing. For example, GA incorporates the concern of problematic medication use. This may entail potentially inappropriate medications or polypharmacy defined by too many medications. [22]

In oncology, a standardized set of tools comprising a GA has gained acceptance with efforts from the Cancer and Aging Research Group (CARG).[23] A composite risk score based on the most important predictors from the CARG GA has been validated to better discriminate the risks of chemotherapy-induced toxicity relative to physician rated PS in a general oncology population.[24] However, the CARG GA risk score was tested in a general oncology population primarily undergoing treatment for solid tumors. The CARG GA cannot be readily applied in older adult HCT populations as many of the adverse factors in the model are not applicable to allogeneic HCT (e.g., GI or GU cancer, polychemotherapy versus monochemotherapy, severe chronic kidney disease and/or anemia). Nevertheless, the toolkit within the CARG GA forms a scaffold to better phenotype age-related heterogeneity in subject fitness prior to transplant. In this protocol, we will build upon the CARG GA, removing non-essential items and adding more sensitive tools (i.e., HCT-CI, frailty phenotype and biomarkers) that offer specific value to the HCT population.

1.6.2 Function and Frailty

Although physician assessed performance status has long been the standard functional element of HCT risk assessment, emerging data underscore the potential utility of more direct measures of

subject function. In a single institutional series in Chicago, among those 50 years and older receiving allografts, 40% had at least one limitation by the Lawton Instrumental Activities of Daily Living (IADL).[21] IADL measures independence in seven areas: managing medications, finances, meals, grocery shopping, telephone, transportation and driving, and housekeeping/chores. In this protocol, the eighth IADL of laundry is excluded as has been done in modern studies using the Older Americans Resources and Services Scale (OARS) IADL scale, including the CARG GA and Chicago based GA (Copyright © 1975 Duke University Center for the Study of Aging and Human Development, used with permission). {Fillenbaum, 1981 #975} Subject reported functional impairments were also common prior to HCT in series from Houston and San Francisco.[25, 26] Although frequently used in general oncology, few studies have explored performance based functional testing to prognosticate allogeneic HCT outcomes. Slow 4-meter walk speed predicted higher mortality in the Chicago series cited above. In studies of adult subjects of all ages, impairments in cardiopulmonary fitness, measured by 6-minute walk distance or cycle ergometry, were able to identify higher mortality risks. [27, 28]

Frailty in older adults is a clinically recognizable state of increased vulnerability to adverse health outcomes such as disability, falls, institutionalization, and death. Frailty is often defined as a medical syndrome that results from age-associated declines across multiple physiologic systems. Function remains a central aspect of frailty determination. The Johns Hopkins Frailty Assessment Instrument, also known as the Physical Frailty Phenotype, is one of the most commonly utilized and cited instruments available for researchers and clinicians. [29] This tool combines physical measurements and questions related to activity and energy levels. The Physical Frailty Phenotype measures five phenotypic criteria: unintentional weight loss, exhaustion, low energy expenditure, low grip strength, and slowed waking speed. [29] A single score that represents these aggregate measures is constructed and provides a classification of frail (score 3-5), pre-frail (score 1 or 2) and robust (score 0). This instrument was designed to maintain validity for frailty syndrome identification while maximizing feasibility and usability in both research and clinical settings.

The physical frailty phenotype has been extensively studied for prognostication in non-transplant older adult populations. [30] In the Chicago study of 203 transplant subjects, around 25% of allogeneic HCT recipients 50 years and older prior to transplant met frailty criteria by the frailty phenotype. [19] However, frailty was not significantly associated with NRM or survival possibly related to a limited sample size completing the Physical Frailty Phenotype (n=38 were frail).

1.6.3 Cognition

Significant cognitive impairment or dementia is associated with older age. A spectrum of cognitive function exists with an intermediate stage between dementia and healthy aging, often termed mild cognitive impairment. [31] Chemotherapy and/or cancer may also induce measurable reductions in cognition. [32] Testing for cognitive impairment ranges from short screening batteries that may include the Blessed Orientation Memory Concentration test and mini-Cog to 3-4 hours of intensive neuropsychological batteries. The Montreal Cognitive Assessment (MoCA) is one of several tests recommended to screen test for global cognition covering domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. [32] The MoCA assessment takes about 10 minutes, has a

maximum score of 30 and a score of less than 26 suggests cognitive impairment.[33] Lowering the threshold below 26 improves sensitivity but reduces specificity in the general population. Many clinicians are more familiar with the Mini-Mental Status Examination (MMSE). As per a recent Cochrane review regarding the MoCA, "…recommend against approaches that use the MoCA in isolation…" . [33] Moreover, the appropriate scores vary substantially with educational level and race/ethnicity. [34] A recent meta-analysis accounting for heterogeneity of studies and populations suggest MoCA threshold of < 23 for mild cognitive impairment (MCI). [35] The recommended threshold to discern between MCI and AD in two studies was < 18 or 19. [36] [37] The MoCA has gained favor over the MMSE as the MoCA is not copyrighted and better gauges executive function. Nevertheless, similar to other cognitive screening tests, one cannot diagnose dementia or the degree of cognitive impairment without clinical correlation. [37].

In HCT, most studies of cognitive function have reported on younger allogeneic HCT recipients. [38] The Houston series of adults 60 years and older utilizing a GA described a 16% prevalence of mild cognitive impairment to transplant. [25] The etiology and consequences of HCT in older adults manifesting cognitive difficulties are not established. However, outcomes of non-transplant intensive chemotherapy for hematologic malignancy is inferior in older subjects found to have cognitive impairment by screening tools compared to those with normal cognition. [39, 40] This suggests mild cognitive impairment should be incorporated in models to better delineate HCT risks in older adults.

Cognitive changes after transplant are of considerable interest. Joint recommendations from the CIBMTR and EBMT highlighted the need for larger prospective studies. [38] The review summarized the post-transplant changes as perhaps some early cognitive changes in the first few months that often return to baseline with considerable individual variation. A meta-analysis of autologous and allogeneic HCT indicated from studies employing formal neuropsychological testing showed no major cognitive changes after transplant. [41] However, the median age of participants across all studies was 42 years. We advocate a simpler approach of repeating the MoCA at day 100. Although data and trajectories in HCT are lacking, studies in the stroke literature have proposed the minimally important difference for the MoCA was 2. [42] [43]

1.6.4 Quality of Life

Quality of life (QOL) refers to every dimension of life except for its length and includes physical abilities, symptoms, social well-being, psycho-emotional status, and spiritual/existential qualities. It reflects how well people feel, what they can accomplish, how satisfied they are with their lives, and whether their lives have meaning and purpose. HCT survivors generally report high global QOL following HCT, but many specific symptoms can contribute to limitations on their daily activities. [44, 45] Longitudinal QOL changes specific to older adults undergoing HCT have been less well studied. The perceived impact of HCT on long term function and QOL can represent a significant barrier to referral by community oncologists, and to subject and family choices in favor of allografting. A more rigorous longitudinal assessment of QOL in this

population will provide better data on which physicians may counsel subjects and families and by which subjects may make more informed choices.

1.6.5 Serum Biomarkers

Serum biomarkers have also been used as prognostic markers prior to transplant. The three biomarkers best studied may be ferritin, albumin and C-reactive protein (CRP). Each marker has a specific clinical predictive utility in routine practice: serum ferritin to gauge iron storage, albumin for nutrition and protein loss, and CRP for infection and inflammation.

Within transplant, pre-conditioning serum biomarkers have emerged to aide in prognostication. Hyperferritinemia has been widely studied with most studies suggesting higher mortality risk for high serum ferritin.[46-48] CRP was originally reported above the median of 18 mg/L as an independent prognostic marker in one study [49] Pavlu showed baseline CRP of 10 mg/L and HCT-CI predicted for worse survival and higher early NRM at day 100 after myeloablative allografting [50] Vaughn reported serum albumin in a large series to be independently prognostic.[48]

A CIBMTR study aimed to validated serum ferritin, albumin and CRP effects on outcome. [51] They found that albumin < 3.5 g/dL and CRP > 10 mg/L independently worsened survival with significant worsening of transplant-related mortality for hypoalbuminemia and borderline significance for high CRP. Serum ferritin above 1000 ng/mL was not prognostic except at markedly high levels above the 90th percentile. These findings argue favorably for including CRP and albumin in any robust composite prognostic model for older adults undergoing HCT.

1.7 Composite Prognostic Models in Older Adults

As highlighted above, optimal prognostication in an older population will likely require consideration of vulnerabilities across health domains and biomarkers. In Geriatric Oncology, composites scores have emerged as the paradigm to predict toxicity utilizing vulnerabilities from a GA and/or biomarkers.[24, 52] Composite scores for HCT outcomes have been created utilizing the HCT-CI plus age, HCT plus IADL, or biomarkers alone. [18, 21, 48, 51] Although predictors have differed, the studies have converged on creating integer-based scoring systems derived from risk factors for clinical ease rounding based on effect size.

Given the unique toxicities and complications of allogeneic transplantation, such as GVHD, validation, and not assumptive application, of the most predictive markers for optimal outcome needs to be undertaken in a large representative cohort. The protocol will create a composite-risk score comprised of the prognostic factors established in transplant and non-transplant studies of older adults discussed in the previous sections.

1.8 Rationale for Development of Composite Model for NRM Prognostication in Older Adults Undergoing HCT through the BMT CTN

This prospective observational study of older allogeneic HCT recipients enables the development and validation of a comprehensive composite health risk assessment model specific to older adult HCT. This study will also shed light on the patient centered outcomes of post-transplant QOL

and functional trajectories. Such a risk assessment tool will immediately impact clinical practice by informing selection of older patients for HCT. Better risk stratification may paradoxically increase use of allografts by overcoming biases against transplant based on the fear of primarily transplant related-mortality and secondarily transplant related-morbidity. Further, the study will equip transplant physicians with an evidence based physiologic aging assessment to better counsel older subjects and families when considering allografting versus other treatment approaches.

This proposal directly fulfills the stated objectives of the BMT-CTN. First, a comprehensive prognostic model specific to HCT would likely increase HCT referral of suitable candidates and ultimately enrollment to BMT CTN trials. Second, the results set the stage for risk-adapted studies testing novel interventional approaches based on the composite health risk assessment score created by this study. This may include more intensive therapies (i.e., ablative regimens, pre-transplant cytoreduction, maintenance, etc.) for older patients at low risk for NRM risk. Conversely, lower intensity approaches and/or geriatric targeted intervention trials would be warranted for those with intermediate to high risk scores pursuing HCT or perhaps other cellular therapy. Third, by facilitating better application of HCT, the risk model would improve HCT outcomes and ultimately improve results for older patients with hematological diseases. Finally, we believe the study instruments may emerge as standards for pre-transplant assessment of older adults and post-transplant trajectories (e.g., post-transplant frailty and disability).

The proposed protocol fulfills a critical unmet need within the transplant field. As more transplants are being conducted for older adults without a clear improvement in NRM in these subjects over time, [8] it is critical that we refine and understand subject selection. A large, complex observational study such as the current proposal is best accomplished through the BMT CTN. Established in 2001, the BMT CTN has the stated goal to conduct large multi-institutional clinical trials addressing important issues in hematopoietic stem cell transplantation. The National Institutes of Health (NIH) request for authorization U24 RFA-HLA 17-019 funded the network states: "The overall goals of the BMT CTN are to improve HCT outcomes, evaluate promising novel cell therapies, and rapidly disseminate study results to improve the scientific basis for the treatment of subjects in need of HCT therapy." (https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-019.html)

The periodic BMT CTN State of the Science Symposia (SOSS) informs the creation of future protocols. In the 2014 BMT CTN SOSS, the Comorbidity and Regimen Related Toxicity Committee proposed the framework for the present protocol hypothesizing "...functional assessment and biomarkers to validated clinical indices will improve the ability to detect NRM and RRT in older subjects".[2] The protocol also follows the guidance to the extent possible from Lee and colleagues on Collection of Subject-Reported Outcomes in BMT CTN trials as summarized in Table 1.8.
(https://web.emmes.com/study/bmt2/public/SOSS/BMT%20CTN%20SOSS%20QOL%20white%20paper%20QOL.pdf)

Table 1.8. Study Design Recommendations-Modified from Lee

Design Recommendations (abbreviated below from Lee)	**Implementation in this study**
Use Similar instruments and assessment points as other BMT CTN studies	Harmonizing correlative samples, QOL tools and QOL collection time points correlative to other CTN studies
Minimize respondent burden	Streamline tools from GA and limit QOL surveys
Collect PRO at important time points	Assessments at clinical milestone visits
Require collection of subject-reported information prior to randomization or confirmation of enrollment	Not applicable-no randomization
Liberal time windows for data collection	Windows for each time point
Inclusion of non-English speakers	Inclusion of Spanish and Mandarin speakers
Subject-reported in schedule of events	Included in schedule
Embed consent for long term follow-up if needed	Will use CIBMTR data and consent for long-term follow-up.

Leveraging the BMT CTN structure will permit expeditiously conducting this trial. Other mechanisms for study design were considered. Embedding the health assessment tools in an interventional study would not enroll an adequate number of subjects and would exclude subjects represented the least fit population albeit those of highest interest. Adding tools to standard transplant center reporting through the CIBMTR would not be feasible for high quality granular data (e.g., cognitive or functional assessment) nor allow cost saving of co-enrollment on other BMT CTN studies. However, once a validated set of tools have been established, future studies can test generalizability across the field of transplant.

CHAPTER 2

2 STUDY DESIGN

2.1 Study Overview

This protocol is a prospective, multicenter, observational and longitudinal study of subjects aged 60 years and older undergoing allogeneic HCT that will develop a pre-transplant composite health score to predict post-transplant NRM at one-year post-HCT.

2.2 Hypotheses and Objectives

2.2.1 Hypotheses

A composite health assessment score combining comorbidities, GA variables, and biomarkers will predict NRM at one year after allogeneic HCT. The composite health score will also define groups with different post-HCT trajectories in health-related quality of life (HRQOL), frailty, nursing-home admissions and disability.

2.2.2 Primary Objective

To determine the set of assessments and biomarkers that could together constitute a robust and valid composite health risk model for accurate personalized estimation of NRM.

2.2.3 Secondary Objectives

To assess the ability of the composite health model to predict the following secondary outcomes at 1 year:

1. Overall survival
2. Cumulative Incidence of Frailty
3. Cumulative incidence of disability
4. Cumulative incidence of admission to a skilled nursing facility
5. HRQOL
6. Cumulative incidence of serious organ toxicity by day 100
7. Cumulative incidence of acute grade 2-4 GVHD at 100 days, 6 months and 1 year and chronic GVHD requiring treatment with systemic immune-suppression at 6 months and 1 year
8. Survival after development of acute grade 2-4 GVHD
9. Cognitive decline at day 100

2.3 Subject Eligibility

2.3.1 Subject Inclusion Criteria

1. Subject is ≥ 60.0 years old at time of enrollment.
2. Hematological malignancy as an indication for allogeneic transplantation.
3. Eligible for allogeneic transplantation based on institutional standards
4. First allogeneic transplant planned. Any conditioning regimen and allogeneic donor is acceptable.
5. Able to speak and read English. Spanish, and Mandarin will be acceptable when sites have ability to perform healthcare provider tests in those languages.
6. Written informed consent

2.3.2 Subject Exclusion Criteria

1. Prior allogeneic HCT

2.4 Treatment Plan

2.4.1 Hematopoietic Stem Cell Transplantation

Subjects may receive any conditioning regimen, any stem cell source (e.g., bone marrow, peripheral blood stem cells, cord blood cells or a combination thereof), any allogeneic donor HLA-match (e.g., matched related, matched unrelated donor, mismatched donors, haploidentical donors) and any disease status. GVHD prophylaxis and supportive care will follow institutional standards. Maintenance therapy to prevent relapse is acceptable. Hematologic malignancy must be the primary indication for allogeneic HCT.

2.4.2 Co-Enrollment

Subjects may participate in other studies as long as they do not interfere with the schedule of testing required in this study. The same measures may be used in different studies (e.g., PROMIS measures for co-enrolled subjects).

2.4.3 Language

Enrollment of subjects who do not speak and read English but can speak and read Spanish or Mandarin will be acceptable when a site has staff who are qualified to consent and administer the health care provider tests (e.g., MoCA, grip strength, walk speed etc.) in the appropriate language. Each site will be encouraged to open the study to Spanish and Mandarin speaking subjects.

2.4.4 Consent, Enrollment and Evaluable Subjects

Enrollment for the purposes of the study will begin when the subject has completed the consent process. Subjects consenting but who did not undergo HCT will be considered exited from the study on the date this determination is made and will not be considered part of our evaluable

population. Evaluable subjects for the primary and secondary endpoints will be those who receive HCT. All subjects who sign the Informed Consent Form will be counted against the enrollment ceiling. Relapse is an important study outcome and subjects with relapsed disease will remain on the study. Data will continue to be collected from subjects with relapsed disease, to the extent possible, per the study assessment schedule (Table 4.2.4).

2.4.5 End of Study Evaluation

For subjects who enroll but do not pursue HCT, the health care team will provide information on the Study Exit form within Medidata Rave to understand the reasons for not pursuing transplantation including whether completion of study instruments influenced the decision (**Appendix 2.1**, Section 6.2.1). For subjects who undergo HCT and drop-out of the study before one year, no additional testing will be required.

2.4.6 Timing of Studies

The baseline observations must be performed within 21 days prior to the start of the conditioning regimen and ideally as close to starting the conditioning regimen as feasible. Laboratory tests of CRP and albumin must be performed within 14 days prior to the start of conditioning as CRP levels may be susceptible to infection or other complications from disease-based treatment. Testing done outside of this window due to delays in transplant conditioning must be repeated. The benefit of measures accurately reflecting the present health of a subject outweighs the risks of learning effects of repeated measures. However, baseline assessments can only be repeated one additional time for transplant delays otherwise the patient is considered ineligible to participate.

Follow-up assessments at Day 100, Day 180, and Day 365 are anchored to the date of the study-qualifying transplant. In the event that a subject experiences disease progression or relapse after the study-qualifying transplant and requires second allogenic transplant, follow-up assessments will remain anchored to the initial study-qualifying transplant.

2.4.7 Data Capture of Subject-reported Evaluations

Table 4.2.4 summarizes subject clinical assessments over the course of the study. At the Pre-transplant time point, CIBMTR staff will provide site staff with a link to the electronic PRO instrument and a PDF of a paper version. Site staff will administer the PRO electronically or on paper, per subject request. If the PRO is done on paper, site staff will securely email or fax the completed instrument to CIBMTR to be entered into the electronic PRO (ePRO) system. At post-transplant time points, CIBMTR staff will administer the subject reported instruments electronically, or on paper upon subject's request. The number of questions and expected time burden for the subject may vary based on method of delivery. Additionally, each time point has a different number of assessments. The pre-transplant assessment will take 13-20 minutes to complete, the Day 100 will take 7-20 minutes, and the Day 180 and Day 365 will each take 11-17 minutes. The survey times vary based on method of delivery because computerized adaptive testing, used for participants who complete the survey online, has variable numbers of survey items given and time burden.

2.4.8 Physical Frailty Phenotype

We will measure frailty using the Hopkins Frailty Phenotype instrument, developed by Fried [29] in the Cardiovascular Health Study, and validated by Bandeen-Roche and colleagues [53] in the Women's Health and Aging Studies at baseline, day 100, day 180 and day 365. The frailty assessment includes 5 core criteria: 1) measured walking speed; 2) measured grip strength; 3) an exhaustion questionnaire; 4) a physical activity questionnaire; and 5) questions about unintentional weight loss / low body mass index (BMI).

Necessary tools to measure frailty include the following equipment:

- Scale (preferably physician/medical scale) for weight measurement
- Stadiometer (preferably wall-mounted) or other height measurement tool
- Dynamometer (grip strength measurement tool, by Jamar, provided by the study)
- Stopwatch (To time walking speed measurement)
- Tape Measure (To lay out 4-meter walking course for Walking Speed Measurement)

Subject reported Frailty Phenotype: Standardized self-reported questionnaires will be used to capture exhaustion, physical activity, and weight loss as shown in **Appendix 4.** Weight loss pre-transplant reflects the prior year. Weight loss at day 100 and day 180 will be asked for the prior 3 months to reflect time since the prior assessment. At day 365, weight loss will be asked over the prior 6 months.

Health Care Team Frailty Phenotype: Grip strength and 4-meter walk are both measured by the healthcare team. The 4-meter walk is measured at comfortable pace in a normal hallway on a marked course and recorded using stopwatch (2 trials). Grip strength is recorded using a handheld Jamar dynamometer (3 trials). The dynamometer will be provided by the study. Weight and height are also measured.

Scoring: Scoring will be performed centrally following the algorithm from the Hopkins Frailty Assessment Calculator (http://hopkinsfrailtyassessment.org/) to determine a participant's frailty status. In brief, a 5 point score is generated from each core criteria. Frail (1 point) or not frail (0 points) is assigned for each core criteria. A score of 1-2, or 3-5 results in classification as pre-frail or frail, respectively. Walk speed will also be used as predictor variable at baseline using a threshold different from the frailty index (Table 5.9.1).

2.5 PROMIS Domains

Three PROMIS domains, Depression, Anxiety and Physical Function will be used to measure detailed functioning and symptom burden for subjects. They will be evaluated at baseline, day 100, day 180 and day 365. For each of these measures, higher scores indicate a higher symptom burden.[54] Scores are normalized to 50 with a standard deviation of 10, and scores greater than 0.5 times standard deviation (i.e., <45 or >55, compared to the general population) are considered clinically meaningful.

When delivered on paper, the domains will be delivered in 8-item short forms. When delivered electronically, the domains will be delivered as Computer Adaptive Tests (CAT), in which the questions a person answers are tailored to that person. Each response is used to further refine the

questions a participant receives, and thus the participant's score, for that domain. The PROMIS CAT item banks for a domain typically involve 4-12 items. The first item administered is usually in the middle of the range of function or severity for that domain. After a participant responds, an estimated score is calculated. The PROMIS CAT algorithm then selects the best item in the item bank for refining the estimated score and recalculates the participant's score as they continue responding. The PROMIS CAT continues to administer items until a specified level of measurement precision is reached, or the maximum number of 12 items per measure have been administered. Studies have shown that the average number of items delivered in a CAT domain is 5-8.[55]

2.6 Geriatric Assessment, Additional Tools and Outcome

2.6.1 Demographics

We will ask subjects about their Race, ethnicity, marital/partner status, education, household income, and zip code.

2.6.2 Subject-reported Function

In addition to Frailty Phenotype measures, patients will be asked about their Karnofsky performance status on a decile scale of 0-100% at baseline. At baseline and at all follow-up time points, subjects will be asked 7 questions from the Lawton instrumental activities of daily living (IADL) as seen in **Appendix 4**.

2.6.3 Falls

Subjects will be asked about the number of falls over the past 6 months at baseline and day 365. Falls will be recorded in prior 3 months on days 100 and 180.

2.6.4 Facility Admissions

Subjects will be asked about admission to skilled facilities inclusive of nursing-homes and rehabilitation. This will cover the prior 3 months on days 100 and 180 and the prior 6 months at baseline and day 365.

2.6.5 Physician Questionnaire

Physician's prognostic questionnaire will be requested from the treating physician to estimate survival and utility of a risk score for a given patient at baseline. (See **Appendix 2**). For subjects who do not pursue HCT, an end of study question will be requested of physicians on the study exit form to understand the reasons (e.g., disease progression) as seen in **Appendix 2**.

2.6.6 Laboratory testing

Standard of care laboratory testing in the 14 days prior to conditioning will include a high sensitivity serum CRP and albumin at the local laboratory. CRP assays at each institution vary. The assay should have a lower limit of sensitivity of < 3 mg/L or less.

2.6.7 Cognition

The Montreal Cognitive Assessment will be asked by the health-care team at baseline and at day 100 (See **Appendix 4**).

2.6.8 CIBMTR forms

CIBMTR Comprehensive Report Forms (CRF) will be requested for all subjects enrolled on this trial and data will be used for assessment of pre-transplant clinical status and clinical outcomes. At baseline, we will extract HCT-CI and provider rated KPS. Post-transplant forms will capture acute and chronic GVHD, relapse, and survival over 1 year. Organ toxicity by day 100 will be extracted as below.

2.6.9 Serious toxicity by day 100

The CIBMTR form 2100 includes items that relate to infection and organ toxicity. An aggregate measure of any serious morbidity (yes or no) will be generated to calculate the incidence of serious toxicity by day 100.

The following conditions will be considered serious toxicity if the corresponding questions are answered in the affirmative. (Table 2.6.9)

Table 2.6.9: Study-Related Serious Toxicities

CIBMTR Form 2100 Question Number	Corresponding Condition
439	Septic shock
486	Endotracheal intubation or mechanical ventilation
498	Development of Veno-occlusive Disease (VOD)
500	Cirrhosis
518	Thrombotic microangiopathy (TMA) requiring therapy
528	Need for dialysis
543	Congestive heart failure
546	Coronary artery disease
548	Myocardial infarction/unstable angina
553	Deep Vein Thrombosis or Pulmonary Embolism
556	Central Nervous System hemorrhage
558	Non-infectious encephalopathy
562	Seizures
564	Stroke
574	Pancreatitis
586	Osteoporotic fracture

2.7 Notification to subject or health care team of testing results

The decision to pursue transplantation is complex and requires weighing the potential for disease control against risks to the subject from the procedure. This study enrolls subjects eligible based on institutional standards where the subject and the treating team have elected to pursue allogeneic transplantation. Protocol submitted data that is not collected at the transplant center will not be returned to the treating center. Specifically, for subject reported data related to emotional health, the following message will be included: "The information you provide on this survey is being collected for research purposes only. Individual survey answers will not be shared with your medical care team. If you have concerns about any of the topics this survey asks about, please reach out to your care team for support."

Likewise, as subjects are required to be competent as deemed by the treating physician, and the MoCA cognitive test is only a cognitive screen, we do not specify a threshold whereby specific actions must occur. However, subjects and the team will not be blinded and may utilize the available information. While in other populations, a MoCA score of < 23 may suggest memory impairment, we actually, lack data in this population of patients medically cleared for allogeneic transplant. Therefore, local transplant physicians should follow their standard of care approaches in clearing patients for transplant. [35] [37] Since results from MoCA will be available to the local clinical team, they can use the generated information as they see fit in guiding clinical decision-making or referral for their patients.

Blinding the treating team from protocol generated data is not practical as that some of the testing must be performed at the center by the healthcare team and some patients will complete information on paper. This may also generate questions from the patient. No standard of care exists on how to use the information generated from the study tests before an allogeneic HCT. Institutional standard of care should dictate if and how to utilize protocol generated data. As GA is recommended in some general oncology guidelines, the site will not be encouraged nor prohibited from incorporating information in the medical record.

2.8 Correlative laboratory samples

The study will not collect correlative laboratory samples. However, the unique clinical data from this study forms a rich dataset for future exploration of correlative samples. Therefore, we will encourage the study team to offer the CIBMTR "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries." to patients.

CHAPTER 3

3 STUDY ENDPOINTS

3.1 Primary Endpoint

NRM is defined as death without relapse or progression of the primary hematologic malignancy within the first year of allogeneic transplantation. Relapse will be considered a competing risk and will be defined as per the CIBMTR definition for each hematologic malignancy.

3.2 Secondary Endpoints

3.2.1 Overall survival within 1 year

Overall survival is defined as death from any cause within 1 year of transplant. Surviving subjects will be censored at the date of last follow-up.

3.2.2 Development/Progression of Frailty (DPF)

Frailty will be measured at baseline, day 100, day 180 and day 365 by the 5 component Hopkins frailty phenotype (5 points total, score of 3 or more is frail). Of note, weight loss at day 100, day 180 and 365 will be scored from the prior time point for the purposes of this study rather than 1 year weight loss. DPF at 1 year is defined as an increase to a score of 3 or more (i.e., frail) in subjects who are not frail at baseline, or an increase in the frailty score of one or more points in those who are already frail at baseline. Subjects who miss assessments will be considered censored at the date of last follow-up. Death prior to development/progression of frailty will be considered a competing risk.

3.2.3 Development/Progression of Disability

Modified (omitting laundry) Lawton (i.e., OARS) instrumental activities of daily living (IADL) assessment will be measured at baseline, day 100, day 180 and day 365. [56] Disability is defined as any assistance needed for a specific IADL domain. Development/Progression of Disability will be measured by loss of an additional IADL from baseline (i.e. worsening of disability score by 1 or more IADL) within 1 year. Subjects who miss assessments will be considered censored at the date of last follow-up. Death prior to development/progression of disability will be considered a competing risk.

3.2.4 Facility Admission

Facility admission will include any overnight stay in a skilled nursing facility outside of the hospital. Facilities include rehabilitation, subacute rehabilitation and nursing-homes. Generally, such admissions occur as discharges from the hospital setting. Residing at home with a nurse or paid caregiver would not be considered a facility admission. Transfer of care to a rehabilitation center within the same hospital or organization would also be considered a facility admission for

the purpose of the protocol as this implies the subject was not well enough to live independently. The study chairs should be contacted to reconcile ambiguities.

Facility admission will be measured for the prior 3 months at day 100 and day 180 and the prior 6 months at day 365. The cumulative incidence of first admission to a facility as well as the rate of admissions accounting for recurrent admissions will be calculated over one year.

3.2.5 Development of cognitive decline

The MoCA will be performed at baseline and day 100. Cognitive decline will be defined as a 2 point or greater decline from baseline on the total score at the day 100 re-evaluation. Cognitive decline will be assessed in all patients in subgroups who do and who do not have relapse of their malignancy prior to day 100.

3.2.6 Health Related Quality of Life

PROMIS Global Health Physical Function, Anxiety and Depression will be measured at baseline and then at day 100, day 180, and day 365.

3.2.7 GVHD

Acute and chronic GVHD are graded according to CIBMTR Standard Operating Procedures. The cumulative incidence of acute grade 2- 4 GVHD, grade 3-4 GVHD within 1 year, and chronic GVHD over 1 year will be measured.

3.2.8 Serious organ toxicities by day 100

Affirmative answers to select questions on the CIBMTR forms will constitute the presence of serious organ toxicity (Table 2.6.9). The cumulative incidence by day 100 will be calculated.

3.2.9 Survival after development of acute grade 2-4 GVHD within 1 year of transplantation.

Survival will be calculated from the time of onset of grade 2 or higher acute GVHD until 1 year.

CHAPTER 4

4 SUBJECT ENROLLMENT AND EVALUATION

4.1 Enrollment Procedures

4.1.1 Approaching Subjects

Subjects may be approached for enrollment when considering allogeneic transplantation if they are expected to be age 60 years or older at the time of enrollment. Eligibility criteria will be verified, and ineligible subjects will proceed off study and no study procedures will be conducted. Eligible subjects willing to potentially participate in the trial will have a thorough discussion about the protocol with the study staff at their institution.

As this study carries low potential risk for harms, this discussion may take place by telephone to prepare subjects for the consent visit and study procedures. Telephone discussion will reduce barriers underscored by Hurria and colleagues such as distance from the center, costs of additional visits, or functional compromise. [57] This telephone discussion also will benefit subjects by improving the efficiency of the study visit by allowing the study team to prepare materials and allowing the subject to allot adequate time. Study testing and procedures will only occur after written informed consent.

Subjects will be considered enrolled once informed consent is obtained. Subjects will be registered using the EDC System Medidata Rave. Prior to initiation of the study specific activities, an authorized user at the transplant center will complete the enrollment forms in Medidata Rave.

4.1.2 Monitoring Accrual

Subject enrollment and accrual among older adults will be monitored at each participating site. The goals are to accrue a high proportion of eligible subjects at each participating center, to meet overall accrual goals and to have a diverse representative population. Centers not enrolling a high proportion of eligible subjects will be contacted to determine whether there are barriers in approaching subjects.

4.1.3 Age

We aim to have high representation of the oldest subjects, with those 70 years and older representing 20% of the enrolled study population. Present estimates suggest ~20% of subjects 60 years and older treated at BMT CTN centers are 70 years or older (unpublished CIBMTR data). In monitoring accrual, the study team will review overall protocol accrual and center specific accrual by age (60-69 and 70 and older) including potentially eligible but not accrued patients through CIBMTR data of patients undergoing allogeneic HCT. Recruitment methods may be reviewed and adjusted if needed to accommodate additional subjects 70 years or older.

4.1.4 Affiliate Centers

Affiliate centers will be encouraged to participate, with the expectation that a high proportion of subjects who are eligible will be enrolled at the site to ensure broad representation.

4.2 Study Monitoring

4.2.1 Follow-up Schedule

The follow-up schedule for study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the BMT CTN 1704 Rave CRF (Case Report Form) Completion Guide.

Table 4.2.1: Schedule for Study Visits

Study visit	Time point	Target Day Before and After Transplant
1	Baseline	0 - 21 days prior to first day of conditioning*
2	100 day	100 -14/+21 days
3	180 day	180 ± 28 days
4	365 day	365 ± 28 days

* 14 days for biomarkers (CRP, Albumin)

4.2.2 Case Report Forms

4.2.2.1 Criteria for Forms Submission

Criteria for timeliness of submission for all study forms are detailed in the CRF Completion Guide. Forms that are not entered into Medidata Rave within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into Medidata Rave and/or a Protocol Deviation Form is completed.

4.2.2.2 Reporting Subject Deaths

Recipient death information must be entered into Medidata Rave within 7 days of knowledge of the subject's death. If the cause of death is unknown at that time, it does not need to be recorded at that time. However, once the cause of death is determined, the Study Exit Form must be updated in Medidata Rave. Although death is unlikely to be related to study participation, immediate notification is also necessary to avoid the central study staff contacting a subject who is deceased.

4.2.2.3 CIBMTR Data Reporting

Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants (defined as receiving the first dose of pre-transplant conditioning whether or not a graft infusion is performed) done at their institution during their time of participation to CIBMTR. Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires

submission of these forms for all US allotransplant recipients.) Enrollment on BMT CTN #1704 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post-transplant Comprehensive Report Forms must be submitted for all subjects enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Forms Submission Schedule. Subjects not undergoing HCT are not required to have their information reported to the CIBMTR.

4.2.2.4 Outcomes

Standard transplant outcomes including relapse, GVHD, toxicity and survival will be reported to the CIBMTR on post-transplant Comprehensive Report Forms per the standard CIBMTR schedule for the submission of these forms. For scheduling of study visits, a target day range has been provided in Table 4.2.1.

4.2.3 Adverse Event (AE) reporting

Reportable adverse events in this protocol are only those unexpected serious adverse events (SAEs) that are directly linked to study instruments, including study specific tests, (i.e. walk speed or grip strength), or completion of the study questionnaires. Toxicities related to transplant but unrelated to the study instruments are not considered adverse events from this study and do not require study specific reporting beyond what is routinely reported in FormsNet to the CIBMTR per standard practice. The events that are reportable will be reported through an expedited AE reporting system via Medidata Rave.

Risks of study participation include emotional distress from uncomfortable questions, fatigue, and the subject or study team being aware of a limitation from the study instruments that they would not normally be aware of. Risks of a blood draw include pain, infection and bleeding.

4.2.4 Subject Evaluations

Table 4.2.4 summarizes assessments over the course of the study.

Table 4.2.4: Study Assessments

Study Assessments / Testing	Healthcare Team (H) or Subject Report (P) or Lab (L)*	Baseline (Pre-conditioning)	Day 100 -14/+21 (abbreviated survey)	Day 180 +/- 28	Day 365 +/- 28
Subject report					
Race/ethnicity, education, income, demographics	P	X			
Karnofsky performance status (KPS) by subject	P	X	X	X	X
PROMIS Physical function domain	P	X	X	X	
PROMIS Depression domain	P	X	X	X	X
PROMIS Anxiety domain	P	X	X	X	X
Facility admissions[3]	P		X[5]	X[5]	X[5]
OARS IADL [1]	P	X	X	X	X
Falls	P	X	X[5]	X[5]	X[5]
Frailty phenotype - Weight loss[2]	P	X	X[5]	X[5]	X[5]
Frailty phenotype - Exhaustion[2]	P	X	X	X	X
Frailty phenotype- Activity level[2]	P	X	X	X	X
Number of medications for polypharmacy	P	X			
Healthcare team report					
Frailty phenotype - Walk Speed, 4 meter[2]	H	X	X[7]	X[7]	X[7]
Frailty phenotype- Grip Strength[2]	H	X	X	X	X
Montreal Cognitive Assessment (MoCA) for cognition	H	X	X[7]		
CIBMTR Forms	H	X	X	X	X
Physician Prognostication Questionnaire	H[8]	X			
Early End of Study Questions (as needed) [6]	H	X			
Laboratory Testing					
CRP[4]	L	X			
Albumin[4]	L	X			

*To be performed within 21 days prior to start of conditioning. If multiple values, enter value closest to conditioning.

1 OARS IADL 7 questions, omit "laundry" from Lawton IADL
2 Fried Frailty phenotype (5 point index). Subject report domains are weight loss, exhaustion and activity level and health care team reports walk speed and grip strength.
3 Overnight admission to any facility including nursing-home, subacute rehabilitation
4 Standard of care laboratory tests. Must be performed within 14 days prior to start of conditioning.
5 The time period for day 100 and day 180 questions will be the prior 3 months and at day 365 the prior 6 months.

6 For those who enroll but do not pursue transplantation

7 Assessment may be conducted remotely, as described in Appendix 6.3.3. if it is not feasible to conduct the assessment in-person.

8 Physician Prognostication Questionnaires completed >30 days after date of transplant will be considered missing. A protocol deviation should be submitted if the questionnaire is not sent to the provider prior to conditioning, is sent to the provider after initiation of the conditioning regimen, or if the questionnaire is not completed, but does not need to be submitted if the questionnaire is returned late by the provider (i.e., is completed by the provider after initiation of the conditioning regimen).

4.2.5 Subject-reported data capture

At the time a subject enrolls in the study, the CIBMTR Survey Research Group (SRG) is notified and then adds that subject to CIBMTR's electronic Subject Reported Outcomes (ePRO) system for data collection tracking.

Pre-transplant subject-reported data will be collected by the center electronically or on paper forms within 21 days prior to the start of conditioning. If conditioning is delayed, the subject-reported surveys should be repeated so they are within 21 days of start of conditioning. Electronically collected pre-transplant instruments will be directly entered in the ePRO system via unique links. The center will securely email or fax pre-transplant instruments completed on paper to the SRG to enter into their electronic ePRO system. Along with the pre-transplant instruments, the center will complete the required forms in FormsNet prior to the 100 day visit so that the SRG can reach the subject for all post-transplant time points.

The SRG will administer the 100 day, 180 day and 365 day instruments online, or on paper if requested by the subject. The SRG will first confirm each subject's clinical status with the transplant center because reporting of deaths may lag. The SRG will then contact the subject via email, phone or mail to collect the subject reported information online or on paper. The SRG will follow-up with non-responders to minimize missing forms. Data will continue to be collected even if the subject has relapsed disease and/or undergone treatment for relapse to the extent feasible.

- 100 days -14/+21 days
- 180 days +/- 28 days
- 365 days +/- 28 days

At the conclusion of each subject reported data collection, subjects will be reminded of the next date of contact. The SRG will notify the transplant center if a subject's contact information has changed or if they find through follow-up that the subject has died, and centers will be required to update and enter Rave forms accordingly.

4.2.6 Quality Control:

This protocol includes tools that must be administered by a health care team member (e.g., research coordinator, nurse etc.) such as walk speed, grip strength and cognition. Standardized administration of these tools across sites will reduce measurement error and improve generalizability of results. Therefore, site staff administering these tests will be required to attend mandatory training. Video training will also be made available to view. A log of trained users

will be maintained by the protocol team. Specifically, regarding the MoCA assessment, each site should have a "super-user" who has completed online certification and can also train other staff to perform the testing.

CHAPTER 5

5 STATISTICAL CONSIDERATIONS

5.1 Study Design

This study is a prospective observational longitudinal study of subjects 60 years and older who are offered allogeneic HCT for treatment of hematologic malignancies. The primary objective is to design and validate a composite health assessment risk model (CHARM) to predict NRM within 1-year after allogeneic HCT. This model will incorporate the impacts of statistically important subject-related variables that could include components of the GA, frailty, comorbidity burden per the HCT-CI, and various biomarkers. We will then use the composite health assessment risk model (CHARM) to describe differences in trajectories of secondary outcomes of quality of life, frailty, nursing-home admissions and disability among groups of subjects with different scores.

5.2 Accrual and Study Duration

In 2012-2016, there were 2870 subjects transplanted in BMT CTN Core Centers and 1648 transplanted in active Affiliate Centers who were 60 years and older and undergoing first allogeneic HCT for hematologic malignancies. This translates into a total of 4,518 subjects aged 60 years and older given allogeneic HCT at both Core and Affiliate BMT centers for an annual number of about ~900 subjects. With the consistent annual increase in number of older subjects given allogeneic HCT, we anticipate the actual annual number to be closer to 1000 subjects during the conduct of this study.

We expect the study to be open at all BMT CTN Core Centers (except for the Pediatric BMT Consortium) in addition to a selected group of Affiliate Centers. We anticipate that the number of centers that will open the study will make it available for ~90% of the 1000 subjects, for a total of 900 annual subjects.

Second, we anticipate that among the approximately 900 subjects aged 60 years or older offered allogeneic HCT at these centers, we estimate 60% to be enrolled and sign consent form for a total of 550 subjects. While this number is higher than usually assumed for BMT CTN trials, it is justified here given the observational (non-interventional) nature of this study, the few exclusion criteria, and the fact that most of the transplantation procedure will follow standard center practice. Given the possibility of change in transplant indication or timing, we anticipate about 20% of that sample (n=550) will not proceed to transplant and hence will not contribute to final model design. The remaining sample (80%) expected to receive the transplant and hence contribute to model development is about 440 subjects annually.

Assuming 440 subjects enrolled and given HCT per year, which is about 37 subjects per month, the study will require 24 months to recruit the target sample size of n=880 subjects. This is similar to the accrual rate for BMT CTN 0902, a similarly inclusive and minimally burdensome protocol which accrued 711 subjects over 18 months. All subjects will be followed for a

minimum of 1 year; therefore, the total study duration is expected to be 3 years. Subjects who do not complete all baseline assessments will continue to be followed. The proportion of patients who do not go on to transplant will be monitored. If the proportion is substantially higher than expected (20%) we will explore the reasons why and consider adjusting the accrual period needed to reach 880 evaluable patients.

5.3 Primary Endpoint

The primary endpoint is NRM at 1 year. NRM is defined as time to death without evidence of disease progression or recurrence from transplant. Disease progression or recurrence will be considered competing events. Subjects alive without progression or recurrence will be considered censored at the date of last follow-up.

5.4 Primary Hypothesis

A validated composite health risk assessment score comprising a combination of comorbidities, one or more components of a GA, and biomarkers will optimally risk-stratify mortality within one year after allogeneic transplant.

5.5 Sample Size and Power Considerations

Sample size calculation is based on the ratio of the number of NRM events divided by the number of potential (candidate) predictors. This ratio is known as events per variable or simply EPV. An EPV in the range of 10-15 is widely advocated as a rule of thumb for Cox proportional hazards regression models with higher EPV recommended when there are predictors with low prevalence. Concato et al. and Peduzzi et al. encouraged the use of an EPV of at least 10 for Cox regression-based prediction models. [58, 59] Ogundimu et al. recommend using EPVs greater than 10 to calculate sample size especially when low-prevalence predictors are present in a model to eliminate bias in regression coefficients and improve predictive accuracy. [60] Since we expect modest prevalence of our proposed predictors of 15-40%, we will use an EPV of 12. The NRM rate in our subject population is estimated to be 22% (upper limit of the 95% confidence interval) based on CIBMTR data for Core and Affiliate Centers. There are 13 variables to be tested for inclusion in the model and an additional 3 variables for adjustment with a total of 16 variables. Per the equation: (N x 22%)/16= 12 EPV, we will need a sample size of 880 subjects. We will use this entire cohort to develop our model. [61] To provide additional support for the sample size calculation beyond the events per variable approach Table 5.5 was created. Given a sample size of 880 patients, under a simple Cox regression model with a single binary predictor, we will have 80% power to detect the hazard ratios as shown in Table 5.5 using a two-sided score test with a significance level of 0.05 assuming a R-square of 0.30.

Table 5.5. Detectable Hazard Ratios for Each Binary Predictor

Estimated frequency of binary predictor	0.15	0.20	0.25	0.30	0.40
Hazard ratio	1.96	1.83	1.75	1.69	1.63

5.6 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all subjects. In addition to the variables being utilized for the risk score development in Table 5.9.1, other characteristics to be examined are: age, gender, race/ethnicity, primary disease, disease- specific risk categories per Disease-risk index (DRI), donor type and HLA matching, stem cell source, donor/recipient CMV status, donor/recipient sex match, and intensity of conditioning regimen.

5.7 Analysis of Primary Endpoint

5.7.1 Analysis of the Primary Endpoint

Incidence of NRM at Days 100, 180 and 1 year will be estimated using the cumulative incidence estimate, treating disease relapse or progression as a competing event. The primary method for building a composite health risk assessment score to predict NRM will be based on using a multivariate Cox proportional hazards regression model for the cause-specific hazard of NRM. We will fit this predictive model with potential covariates as described in Table 5.9.1 and explore different cut-points for predictors. Proportional hazards assumptions will be assessed for each variable using graphical approaches and time-dependent covariates; if proportional hazards are violated, time-dependent covariates will be used. Variable selection for the Cox regression model will be done using a step-wise model building approach for all multivariate models. After stepwise variable selection is complete, we will further assess the contribution of each of the final variables selected in the model to the predictive performance. This will be done by computing C-statistics and Brier scores for this final model, as well as simpler models obtained by dropping one variable at a time. We will use this information to assess whether further pruning of the variables in the risk score is indicated due to lack of contribution to predictive performance despite statistical significance.

A composite health risk score will be constructed from the final Cox model by summing the log hazard ratios for each of the relevant covariates to be included in the scoring system. We will also consider approximating the score by replacing the log hazard ratios with a numeric scoring system for ease of clinical use and will consider the creation of up to 3 groups based on tertiles of this score to facilitate summarizing the effects through cumulative incidence curves by group. The following baseline variables will be kept/forced into the multivariate model during the modeling process: donor type and HLA matching, donor/recipient CMV status and intensity of conditioning regimen. While these baselines variables will be used to adjust the multivariate model, they will not contribute to the scores created for the final CHARM. Specifically, we will only use the linear predictors ($X\beta$ terms) corresponding to the variables from Table 5.9.1 to construct the final CHARM score. Other baseline variables, as mentioned before, will be included in the multivariate regression model to account for additional differences in risk related to transplant or donor matching issues but not used to construct the CHARM score. We anticipate that there will be missing data among the CHARM variables. Therefore, multiple imputation methods may be used before developing the CHARM score.

Although the Cox regression model will be the primary method of analysis, we plan on investigating an alternative secondary prediction model using machine learning techniques such as CoxBoost.[61] CoxBoost utilizes boosting along with a flexible penalization of covariates to build prediction models for survival and competing risks data in a proportional hazards

framework. It can handle potentially high-dimensional and diverse clinical and biomarker covariates. The number of boosting steps and the number of path algorithm steps will be tuned through cross-validation. The original bootstrap is not a particularly good estimator for cross validation. Therefore, we will compare and contrast the prediction performance of the primary and secondary models using 632+ bootstrap cross-validation as detailed below. [62] The 632+ bootstrap is a weighted average of the leave-one-out bootstrap estimator and the naïve estimate of prediction error using weights 0.632 and 0.368, respectively.

5.7.2 Model Validation

A common way to estimate prediction error is to randomly split the sample into training and a validation set. The disadvantage of this is that not all data is available for model building and parameter estimation. Instead, we will employ the 632+ bootstrap cross-validation method to estimate the prediction error and explained variation using the approach by Schemper and Henderson. [63]

5.8 Analysis of Secondary Endpoints

Three risk groups will be formed, based on the tertiles of the CHARM risk score. We will provide univariate summaries of each of the secondary outcomes by CHARM score risk group for each endpoint. We will then compare the risk groups multivariate models developed for each outcome separately as detailed below. All the demographic and baseline characteristics described in section 5.6 above will be considered via stepwise variable selection for inclusion in the model. Assuming an overall type I error of 10%, a significance level of 1% will be used for all secondary analyses based on Bonferroni adjustment since we will be considering 10 endpoints between section 5.8.1 and 5.8.9. A sensitivity analyses will also be done base on the CHARM score as a quantitative measure rather than tertile groups.

5.8.1 Overall Survival

Kaplan-Meier curves will be constructed to estimate overall survival probabilities. A multivariate Cox regression model for the risk of death will be developed to estimate hazard ratios for the CHARM risk groups after adjustment for baseline characteristics as described above.

5.8.2 Development/Progression of Frailty (DPF)

Frailty will be summarized at each time point using descriptive statistics. Incidence of DPF up to 1 year will be estimated with 95% confidence intervals using the cumulative incidence estimate, treating death prior to DPF as a competing event. A multivariate Cox regression model for the cause-specific hazard of DPF will be fit to estimate hazard ratios of the CHARM risks groups after adjustment for baseline characteristics as described above. Additionally, we will develop a separate Cox model using individual predictors rather than the overall CHARM score in order to assess the relative importance of the predictors in Table 5.9.1 on DPF and compare to CHARM predictive power for DPF.

5.8.3 Development/Progression of Disability (DPD)

Incidence of DPD up to 1 year will be estimated with 95% confidence intervals using the cumulative incidence estimate, treating death prior to DPD as a competing event. A multivariate

Cox regression model for the cause-specific hazard of DPD will be developed to estimate hazard ratios for the CHARM risk groups after adjustment for baseline characteristics. Available disability scores for survivors at specific time points will be summarized using means and standard deviations. Patterns of missing disability score over time will be examined using graphical techniques and logistic regression models. At each time point, the effect of CHARM risk group and other baseline covariates on the mean disability score conditional on being alive at that time point will be estimated using the inverse probability of censoring-weighted generalized estimating equations with independent working correlation model of Kurland and Heagerty.[64] Multiple imputation methods may also be used. Additionally, we will develop a separate Cox model using individual predictors rather than the overall CHARM score in order to assess the relative importance of the predictors in Table 5.9.1 on DPD and compare to CHARM predictive power for DPD.

5.8.4 Admission to a Skilled Nursing Facility

Cumulative incidence of the time to the first facility admission will be described, along with the number of facility admissions per person years of follow up. Time to first admission will be modeled using Cox regression for the cause-specific hazard of admission, in order to compare hazard ratios between CHARM risk groups after adjustment for baseline characteristics. A multivariate proportional rates/means model[65] for the rate of facility admission accounting for multiple admissions will be estimated after adjustment for baseline characteristics, in order to estimate the relative intensities of facility admissions between the CHARM risk groups

5.8.5 Development of Cognitive Decline

The frequency of cognitive decline will be described by creating a change score from baseline to the day 100 evaluation with a score 2 or less from baseline at day 100 reflecting decline. The effect of CHARM risk groups on cognitive decline will be modeled using logistic regression model.

5.8.6 Health Related Quality of Life

Summary of health-related quality of life measures will be scored according to the recommendations of the developers; of primary interest for this study are the summary measures for depression, anxiety and physical function. For the descriptive analysis only, health-related QOL scores for survivors at specific time points will be summarized using means and standard deviations. Patterns of missing health-related QOL data will be examined using graphical techniques and logistic regression models. At each time point, the effect of baseline covariates including the composite health risk score on the health-related QOL outcomes conditional on being alive at that time point will be estimated using the inverse probability of censoring-weighted generalized estimating equations with independent working correlation model of Kurland and Heagerty. [64] Subjects who do not complete all baseline assessments will continue to be followed. Therefore, multiple imputation methods may also be used. These methods will provide adjusted comparisons of mean health-related QOL between CHARM risk groups at each time point conditional on being alive at that time point.

5.8.7 Acute GVHD

Incidence of acute GVHD grade II-IV and grade III-IV up to 180 days will be estimated with 95% confidence intervals using the cumulative incidence estimate, treating death prior to acute

GVHD as a competing event. A multivariate Cox regression model for the cause-specific hazard of acute GVHD will be estimated after adjustment for baseline characteristics. The hazard ratios of the CHARM risks groups in predicting acute GVHD will be compared.

5.8.8 Chronic GVHD

Incidence of chronic GVHD up to 1 year will be estimated with 95% confidence intervals using the cumulative incidence estimate, treating death prior to chronic GVHD as a competing event. A multivariate Cox regression model for the cause-specific hazard of chronic GVHD will be developed to estimate hazard ratios of the CHARM risk groups, after adjustment for baseline characteristics.

5.8.9 Serious Organ Toxicities by Day 100

Serious organ toxicities identified for this study (see Table 2.6.9) will be tabulated by type of toxicity. Number of toxicities and number of patients experiencing toxicities will be described for the first 100 days, as well as the cumulative incidence of any serious organ toxicity by day 100, with death as a competing risk. The CHARM risks groups will be compared for their association with incidences of serious organ toxicities.

5.8.10 Survival after development of acute grade 2-4 GVHD within 1 year

Kaplan-Meier curves will be constructed to estimate survival after development of acute grade II-IV GVHD within 1 year; for purposes of this estimation and analysis, the clock will start at the time of GVHD onset for each subject who develops acute GVHD grade II-IV. A multivariate Cox regression model for the risk of death will be estimated after adjustment for baseline characteristics, in order to compare the hazard ratios of the CHARM risks groups.

5.9 Comparison of characteristics and outcomes between subjects who consented but did not proceed versus those proceeded to HCT

There is a concern of selection bias to transplant influenced by data derived on the individual variables collected from subjects after completing baseline study assessments. We anticipate 20% of those consented for the study and completing some study procedures (i.e., enrolled) may not proceed to transplant due to reasons unrelated to the study such as relapse of primary disease, serious infection or donor issues. Among those who enroll but do not proceed to transplant, we will collect information about the reasons for not proceeding to transplant and describe them. Among subjects enrolled to the study, we will compare those who received versus did not receive the transplant within regards to baseline characteristics as available. Categorical predictors will be compared using chi-square tests and quantitative characteristics will be compared using Mann-Whitney tests. We will not be able to compare outcomes such as survival among consented patients who receive versus do not receive the transplant given the difficulty to collect follow up data on those who do not receive the transplant. It is anticipated that those who fail to receive the transplant because of uncontrolled disease relapse or untreatable infection to have very short survival. Therefore, a better analysis would compare patient characteristics to find out if those who did not receive the transplant had worse features or higher CHARM scores if all CHARM-required tests were done for them.

Table 5.9.1: Potential Variables to Predict Non-Relapse Mortality

Tools	Cut point*	Estimated Frequency (%)	Estimated HR (see footnote 1, 2, 3)	Reference
AGE				
Age	70+	20	1.1[1]	[66], Verbal WS
COMORBIDITY				
HCT-CI	3+	40	1.5[1]	16, 25, 66
FUNCTIONAL STATUS				
KPS by subject	<80%	30	1.4[1]	20, 67
PROMIS Physical Function	<40	40	1.4[2]	21, 68
Instrumental Activities of Daily Living	<14	40	2.3[2]	21
Falls	≥1		1.5[3]	23
4-meter walk[4]	0.8 m/s	25	1.5[3]	[69] (verbal AA and MS)
COGNITION				
Montreal Cognitive Assessment (MoCA)	<26	15	2.0[3]	25 39
PSYCHOLOGICAL STATE				
PROMIS Depression	60	20	1.0[2]	19, 68 70
POLYPHARMACY				
Number of medications (4)	>4		1.5[3]	71
NUTRITION				
Weight loss[4]	≥10%		1.5[3]	71
BIOMARKERS				
CRP	>10 mg/L	25	1.5[1]	51
Albumin	<3.5 g/dL	30	1.5[1]	48, 51

* All thresholds are proposed and may be modified. Falls, weight loss, and polypharmacy do not have adequate data for estimates in transplant populations.

[1] At least two studies support independent value for NRM including at least one study restricted to older adults
[2] At least one study available and/or strong rationale from other work
[3] No reliable data to estimate effects in transplant subjects. Thus, assume HR=1.5 except for cognitive testing where effect size had been larger in non-transplant populations
[4] Will be extracted from the frailty phenotype

Table 5.9.2: TRM and OS 2012-2016 at 100 days and 1 year for all adult patients (aged 60+) with any heme malignancy given 1st allogeneic HCT at BMT CTN CORE and AFFILIATE centers only, stratified by age

	60-64 (N = 1617)		**65-69 (N = 1817)**		**70-74 (N = 704)**		**75+ (N = 81)**	
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**
Treatment related mortality	1537		1761		689		78	
100-day		8 (7-9)%		9 (8-10)%		12 (10-15)%		17 (9-26)%
1-year		18 (17-20)%		21 (19-23)%		26 (22-29)%		29 (19-40)%
Overall survival	1617		1816		704		81	
100-day		88 (87-90)%		87 (85-88)%		84 (81-87)%		81 (72-89)%
1-year		63 (61-66)%		61 (59-63)%		57 (53-61)%		57 (46-68)%

6 APPENDICES

6.1 APPENDIX 1: HUMAN SUBJECTS

1. Subject Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Prinicipal Investigator or his/her designee at each transplant center will contact the candidates, provide the subject with information about the purpose of the study, and obtain consent. The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Institutional Review Board (IRB). The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval to the DCC.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a subject identifier code. The code relaying the subject's identity with the ID code will be kept separately at the center. The ID code will be generated by and kept on file at the BMT CTN Data and Coordinating Center upon enrollment.

3. Participation of Women and Minorities

Women, ethnic minorities, and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of severe aplastic anemia in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

6.2 APPENDIX 2: HEALTHCARE TEAM ASSESSMENTS

Frailty Assessment

Height and weight measurements

1. Current Height: (measured by study staff or patient self-report at follow-up)

2. Current Weight: (measured by study staff or patient self-report at follow-up)

3. Weight 1 year ago:

3 a. If weight loss in past year: "It seems that you have lost weight over the past year. Did you know that you had lost weight?"

- Yes
- No

3 b.If Yes to knowing about weight loss, "Did you lose/gain weight because you were trying to, or not?" (For example, by dieting or exercising)

- Tried to
- Did not try to
- Don't know
- Refused

Grip test measurement

1. "Which hand do you use to sign your name?" (This is the Dominant Hand.)

2. "Have you had any recent pain in your hand or wrist or any acute flare-up in your hand or wrist from conditions like arthritis, tendonitis or carpal tunnel syndrome?"

3. "Have you had any surgery on your hands or arms during the last 3 months?"

3 a. If yes, which hand or arm?

4. Was the grip test completed?

4 a. Record Grip Strength measures (kg) – Measurement 1

4 b. Record Grip Strength measures (kg) – Measurement 2

4 c. Record Grip Strength measures (kg) – Measurement 3

5. If no (Grip Test NOT completed), please mark the reason

Walking Test Measurement

1. Was the walking test completed?

1 a. Time for first usual pace walk (in seconds):

1 b.Time for second usual pace walk (in seconds):

2. If walking speed test was NOT completed, please mark for the reason:

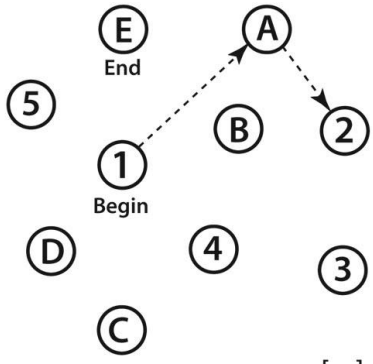
Montreal Cognitive Assessment (MOCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

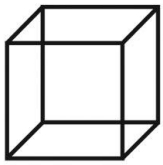
NAME :
Education : **Date of birth :**
Sex : **DATE :**

VISUOSPATIAL / EXECUTIVE — POINTS



[ ]

Copy cube



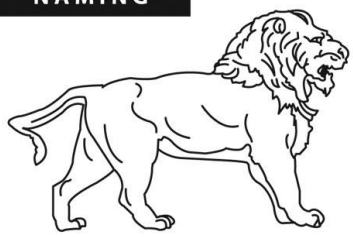
[ ]

Draw CLOCK (Ten past eleven)
(3 points)

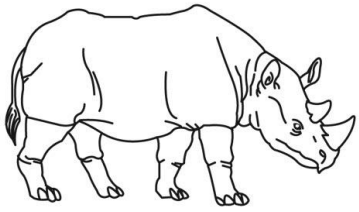
[ ] Contour [ ] Numbers [ ] Hands

__/5

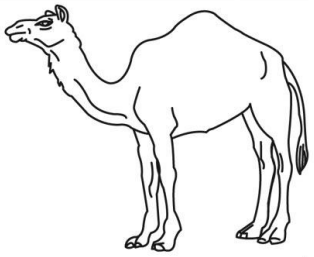
NAMING



[ ]



[ ]



[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

6.2.1 APPENDIX 2.1: PHYSICIAN SURVEYS

Physician Prognostication Questions

1. For the type of transplant that has been chosen for your subject, what do you estimate survival at 1 year will be?

- Very good (more than 90%)
- Good (75-90%)
- Better than 50/50 (50-74%)
- Worse than 50/50 (25-49%)
- Bad (10-24%)
- Very bad (less than 10%)

2. Do you believe an individualized risk assessment tool that predicts 1 year non-relapse mortality based on the subjects' health and fitness would help you to make a recommendation to this subject about pursuing transplant?"

- Yes, better predicting 1 year non-relapse mortality would help
- Yes, but only if the tool also predicts overall survival
- No
- Unknown/don't want to answer

Physician Question for Subject Not Pursuing Transplantation after Enrollment

If subject does not proceed to HCT, please specify reason:

- Disease progression or relapse
- Insurance or economical barriers
- Patient is found to be too frail or too medically infirm per clinical team assessment
- Patient was found to have psychiatric or compliance issues per clinical team assessment
- Patient and/or family do not want the transplant any more
- Patient was found to be ineligible for the study based on information from research-driven tools included in this study
- Other, Specify:

6.3 APPENDIX 3: ASSESSMENT GUIDES AND INSTRUCTION

6.3.1 APPENDIX 3.1: FRAILTY PHENOTYPE GUIDE

Frailty will be ascertained by Physical Frailty Phenotype, which includes the measurement of 5 core criteria: weight loss, walking speed, grip strength, exhaustion, and physical activity. These measures reflect the concept that frailty is a syndrome with multiple criteria needing to be present to constitute being frail. Participants with 3, 4, or 5 components present are determined to be frail. Participants who meet 1 or 2 criteria are pre-frail. Those with none of the 5 components present are non-frail. This frailty assessment instrument consists of the following 5 measures:

1) Measured Grip Strength: Participant attempts to squeeze the dynamometer maximally 3 times with the dominant hand. Measured by a JAMAR hand dynamometer; use maximal score. Meets frailty criterion for grip strength for men if: ≤29 kg for BMI ≤24 or ≤30 kg for BMI 24.1–26 or ≤30 kg for BMI 26.1–28 or ≤32 kg for BMI >28. Meets frailty criterion for grip strength for women if: ≤17 kg for BMI ≤23 or ≤17.3 kg for BMI 23.1–26 or ≤18 kg for BMI 26.1–29 or ≤21 kg for BMI >29.

2) Timed Walking Speed: Participant will walk 4-meter length twice at his or her usual pace. Use average of 2 trials. Meets frailty criterion for slow walking speed for men if: ≤.65m/s for height ≤173 cm (68 inches) or ≤.76m/s for height >173 cm (68 inches). Meets frailty criterion for slow walking speed for women if: ≤.65m/s for height ≤159cm (63 inches) or ≤.76m/s for height >159cm (63 inches)

3) Weight loss: Meets criterion if: Lost >5% body weight unintentionally in last year, or BMI <18.5kg/m^2

4) Exhaustion is assessed using three self-reported items. Meets frailty criterion for exhaustion if answer: Felt unusually tired or unusually weak ‘all of the time’ or ‘most of the time’ or reported energy level was ≤3, from the CES-D Depression Scale. The specific items to be read are:

    1. a. “In the past month, on the average, have you been feeling unusually tired during the day?”
        - Yes or
        - No or
        - Refused or Don’t Know.

    1. b. “If yes, have you been feeling unusually tired:”
        - All of the time or
        - Most of the time or
        - Some of the time or
        - Refused / Don’t Know.

    2. a. “In the past month, on the average, have you felt unusually weak?”
        - Yes or No or Refused or Don’t Know

    2. b. “If yes, have you been feeling weak:”
        - All of the time or
        - Most of the time or

- Some of the time or
- Refused / Don't Know.

3. "Please rate your usual energy level on a scale from 0 to 10 where 0 is no energy and 10 is the most energy that you have ever had. Please give a number between 0 and 10 that describes your usual energy level while awake in the last month?" Record value between 0 and 10.

5) Physical Activity is assess using six self-reported questions from the modified Minnesota Leisure Time Activities Questionnaire related to the amount of activities (and the corresponding task-specific MET intensity scores) that a person performed in a past two weeks. Meets frailty criterion for low activity for men if: <128 kcal of physical expenditure on activity scale per two-week period. Meets frailty criterion for low activity for women if: <90 kcal of physical expenditure on activity scale per two-week period. The MET scores per activity are: walking (w = 3.5), strenuous household chores (w = 4.5), strenuous outdoor chores (w = 4.5), dancing (w = 5.5), bowling (w = 3.0), and exercise (w = 4.5). To compute Kilocalories (kcals) expended per two-week period, use the formula: Kcals/period = w * Frequency (# of sessions in 2 weeks) * Duration per session (minutes) * Body Weight (kg)/60.

6.3.2 APPENDIX 3.2: MONTREAL COGNITIVE ASSESSMENT (MoCA) GUIDE

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

Alternating Trail Making:

Administration: The examiner instructs the subject: *1Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from **I** then to A then to 2 and so on. End here* [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern:

1 – A – 2 – B – 3 – C – 4 – D – 5 – E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the cube: "*Copy this drawing as accurately as you can, in the space below".*

Scoring: One point is allocated for a correctly executed drawing.

Drawing must be three-dimensional

All lines are drawn

No line is added

Lines are relatively parallel and their length is similar (rectangular prisms are accepted). A point is not assigned if any of the above-criteria are not met.

Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a clock. Put in all the numbers and set the time to 10 past 11".*

Scoring: One point is allocated for each of the following three criteria:

Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);

Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;

Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.

A point is not assigned for a given element if any of the above-criteria are not met.

Naming:

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal"*.

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions*: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them"*. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *"I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *"I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them*". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order*." Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.*: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*".

Scoring: Give one point if there is zero to one error (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: *"Now, I will ask you to count by subtracting seven from I00, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 - 85 - 78 - 71 - 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

Sentence repetition:

Administration: The examiner gives the following instructions: *"I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]: *I only know that John is the one to help today."* Following the response, say: *"Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]: *The cat always hid under the couch when dogs were in the room."*

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

Verbal fluency:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike"*. If the subject answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike"*. If the subject does not give the appropriate response *(fruit)*, say, *"Yes, and they are also both fruit."* Do not give any additional instructions or clarification. After the practice trial, say: *"Now, tell me how a train and a bicycle are alike"*. Following the response, administer the second trial, saying: *"Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both; Ruler-watch = measuring instruments, used to measure.

The following responses are not acceptable: Train-bicycle = they have wheels; Ruler- watch = they have numbers.

Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (--) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: Allocate 1 point for each word recalled freely without any cues.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (--) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was, NOSE, FACE, or HAND?"*

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand multiple
VELVET:	category cue: type of fabric	choice: denim, cotton, velvet multiple
CHURCH:	category cue: type of building	choice: church, school, hospital multiple
0AISY:	category cue: type of flower	choice: rose, daisy, tulip multiple choice:
RE0:	category cue: a colour	red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week}."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, and office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all sub scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

MoCA Version August 18, 2010

6.3.3 APPENDIX 3.3: REMOTE ADMINISTRATION OF FOLLOW-UP ASSESSMENTS

This study includes three assessments typically performed in-person at routine visits (Table 1). In-person testing at the time of a routine visit remains the preferred method of testing. However, when not feasible because the subject and/or research team will not be on site, the 4-meter walk and MoCA cognitive assessment can be performed remotely following previously validated methods in small non-HCT populations. Grip strength requires a dynamometer device and thus is not feasible to administer remotely. A protocol deviation will be reported for subjects who are unable to complete this assessment.

Table 1. Summary of In-person Assessments and Timing of Collection

Assessment	Timepoints	Proposed Change
Montreal Cognitive Assessment (MoCA) for cognition	Baseline, D100	Site staff will administer MoCA by audio-visual teleconference. If AV conference is not available, a modified telephone version may be administered.
Frailty phenotype - Walk Speed, 4-meter	Baseline, D100, D180, D365	Site staff will administer 4-meter walk test by audio-visual teleconference. If AV conference is not available, the subject may self-report results of the walk test by telephone.
Frailty phenotype- Grip Strength	Baseline, D100, D180, D365	This assessment will be omitted from remote visits.

6.3.3.1 Remote Montreal Cognitive Assessment (MoCA)

Using audio-visual teleconference, the MOCA can be performed as a virtual bedside test with same elements and score. This follows instructions from the developer (https://www.mocatest.org/remote-moca-testing/). Although preferred as this most likely recapitulates the validity and reliability of an in-person test, a telephone cognitive assessment is an acceptable alternative. Several elements of the MoCA require audio-visual interpretation (trail making, cube, clock, animal naming). However, the remaining elements can be administered by telephone for a total of 22 points (compared to 30 points for the in-person and audio-visual teleconference methods). In one study evaluating the correlation of MoCA and telephone MoCA (i.e., T-MoCA) among patients having a prior transient ischemic attack or stroke in 91 patients, the authors found acceptable reliability for cognitive impairment when considering all domains.[74] Although data are not available for Spanish or Mandarin versions of T-MoCA, the tool used in the primary assessment at baseline (English, Spanish or Mandarin) would be used. Alternative cognitive tools exist (e.g., the 5 minute MoCA) yet employ different questions and thus results cannot be directly compared.[75,76]

MoCA Full Audio-Visual Conference Administration

The rater proceeds as follows.

1. Identify yourself, from which clinic/institution you are from and in which city you are located.
2. Tell the subject the purpose of your call, obtain their verbal consent to proceed.

3. Instruct the subject to get a white sheet of paper, a pencil and an eraser, and to isolate themselves in a quiet room.
4. Show the subject the visual section of the MoCA
    1 **Trails:** Show the subject the Trail and say: "Please **tell me** where the arrow should go next to repeat the pattern I am showing you."
    2 **Cube:** Show them the cube and say: "Copy the cube"
    3 **Clock:** "Draw a clock. Put in all the numbers and set the time to 10 past 11"
    4 **Animal naming**: "Tell me the name of these animals"
5. The rest of the test is done the same way as in the clinic except for the Orientation:
    5 **Date:** "Look straight at the camera and tell me today's date, day of the week, month and year"
    6 **Place:** "From what Clinic/Institution am I calling you from?"
    7 **City:** "What is the city in which our clinic/institution is located?

Telephone MoCA (MoCA-Blind) Administration

The Montreal Cognitive Assessment (MoCA)- BLIND is an adapted version of the original MoCA, a rapid screening instrument for mild cognitive dysfunction. The MoCA-BLIND assesses different cognitive domains: attention and concentration, memory, language, conceptual thinking, calculations, and orientation. It contains the same items as the original MoCA except those requiring visual abilities have been removed. Time to administer the MoCA- BLIND is approximately 5-10 minutes. The total possible score is 22 points; a score of 18 or above is considered normal. This cutoff score is suggestive as it has not been validated thus far.

1-Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions*: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them"*. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *"I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *"I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

2-Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them*". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.*" Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.*: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: *"Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71
– 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

3-Sentence repetition:

Administration: The examiner gives the following instructions: *"I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]: ***I only know that John is the one to help today."*** Following the response, say: *"Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]: ***The cat always hid under the couch when dogs were in the room."***

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

4-Verbal fluency:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or*

words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

5-Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike".* If the subject answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike".* If the subject does not give the appropriate response *(fruit)*, say, *"Yes, and they are also both fruit."* Do not give any additional instructions or clarification. After the practice trial, say: *"Now, tell me how a train and a bicycle are alike".* Following the response, administer the second trial, saying: *"Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
Train-bicycle = means of transportation, means of travelling, you take trips in both; Ruler-watch = measuring instruments, used to measure.
The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler- watch = they have numbers.

6-Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: Allocate 1 point for each word recalled freely without any cues.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was, NOSE, FACE, or HAND?"*

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand
VELVET:	category cue: type of fabric	multiple choice: denim, cotton, velvet
CHURCH:	category cue: type of building	multiple choice: church, school, hospital
DAISY:	category cue: type of flower	multiple choice: rose, daisy, tulip
RED:	category cue: a colour	multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

7-Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 22 points. A final total score of 18 and above is considered normal.

6.3.3.2 Remote Walk Speed Test Administration

Previous studies have shown the feasibility of a home-administered walk test. A self-administered, adapted 6 minute walk time (6MWT) test (the HomeHeart-Walk) had a strong intra-class correlation coefficient (0.98) with a standard in person 6 MWT.[72,73] The test was well

received by participants who had a median age of 64 (range: 49 — 80) years old.[72] The study concluded that self-administered walk test is a reliable and useful method of collecting physical activity data in a medically-challenged, older population.[72] We will implement a similar approach and restrictions used in that study by excluding patients with documented new onset of heart failure, unstable angina pectoris, fever, complex arrhythmia, resting diastolic blood pressure of 100 mm Hg or more or unstable gait from performing the test on their own.[72]

Subjects with documented new onset of heart failure, unstable angina pectoris, fever, complex arrhythmia, resting diastolic blood pressure of 100 mm Hg or more, or unstable gait will not be asked to perform the self-administered walk test. This should be ascertained via medical record review prior to contacting the subject to arrange a remote visit.

The walk speed test should be administered remotely as follows*:

1. Instruct the subject to lay out a 4 meter (13' 1") walking path using a measuring tape.
2. The subject will walk the 4 meter path twice at his or her usual pace.
3. For each walking trial, the amount of time (in seconds) will be recorded. The process by which the walk speed is recorded may be modified based on the circumstances of the remote visit. For example, if the entire walking path is in view of the coordinator, the coordinator may observe the walk test and record time. Alternatively, the subject may record the time (e.g., using the Stopwatch function on a cell phone) and report the results to the coordinator.

   *Variations implemented to remotely conduct the walk speed test will be left to the discretion of the coordinator; however, the walk speed test should be administered twice using a 4 meter walking course (per section 6.3.1. of the protocol).

6.3.3.3 Script for Remote/Virtual Follow-up Visit Coordination & Consent

Hello, this is {your name} from {your institution}. I am calling because you are currently enrolled in the CHARM study. As a reminder, we are doing this study to learn how well patients do after transplant, based on their health before transplant. An important part of this study is following up with you after your transplant to do a walk speed test, grip strength test, and a test of your thinking. Normally we would do these tests during an in-person visit in the hospital or clinic. However, because of the extra safety precautions we are taking due to COVID-19, we will not be able to do these tests in person.

[**Day 100 Visits**] We can do the walk speed test and the test of your thinking while you are at home. We can do these tests using {site-specific language, describe the full audio-visual teleconferencing platform here}. To complete these tests using {site-specific technology}, you will need {site-specific language, describe what the subject will need for the teleconference}. These tests will take about 15-25 minutes to complete. Would you be willing to schedule a time* to complete these tests?

> *If yes*: Schedule time/date of visit. Ask the subject if they have a piece of paper to write down a list of items they will need for the visit. Inform the subject that they will need to

have a piece of white paper, a pencil with eraser, and a quiet place to complete the test of their thinking. For the walking test, subject will need to measure a 4 meter (13' 1") path. If the subject does not have access to a measuring tape, the site will send the patient a tape measure or provide it during a clinic visit.
If no: We can do the tests of your walk speed and thinking by telephone. Would you be willing to schedule a time to complete these tests?

If yes: Schedule time/date of visit. For the walking test, they will need to measure a 4 meter (13'1") path. If the subject does not have access to a measuring tape, the site will send the patient a tape measure or provide it during a clinic visit.
If no: Thank the subject for their time and end call.

[**Day 180, Day 365 Visits**] We can do the walk speed test while you are at home. We can do this test using {site-specific language, describe the full audio-visual teleconferencing platform here}. To complete these tests using {site-specific technology}, you will need {site-specific language, describe what the subject will need for the teleconference}. This test will take about 5-10 minutes to complete. Would you be willing to schedule a time to complete this test?

If yes: Schedule time/date of visit. For the walking test, subject will need to measure a 4 meter (13' 1") path. If the subject does not have access to a measuring tape, the site will send the patient a tape measure or provide it during a clinic visit.
If no: We can do the walk speed test by telephone. Would you be willing to schedule a time to complete the walk test?

If yes: Schedule time/date of visit. For the walking test, they will need to measure a 4 meter path. If the subject does not have access to a measuring tape, the site will send the patient a tape measure or provide it during a clinic visit.
If no: Thank the subject for their time and end call.

*Scheduling a visit in advance is recommended to give the subject time to prepare; however, the visit can be completed in the same call/encounter if feasible.

[**Consent to Proceed**] Before we begin, I would like to confirm with you that you understand that the purpose of this call is for us to conduct test(s) as part of your participation in the CHARM study, and that you are comfortable with proceeding.

6.4 APPENDIX 4: SUBJECT/PATIENT REPORTED ASSESSMENTS AND SUBJECT/PATIENT REPORTED OUTCOMES (PRO)

The following table lists all subject reported assessments to be collected, including the number of items and estimated time to complete at each time point. This appendix also includes all items/questions included on each subject reported assessment. For some assessments, language has been modified to fit administration electronically or on paper, as opposed to in person. Any modifications are noted in the below sections.

Study Assessments / Testing	**# of items**	**Minutes**	**Baseline (≤21 days Pre-conditioning)**	**Day 100 -14/+21**	**Day 180 +/- 28**	**Day 365 +/- 28**
Karnofsky performance status by subject	1	<1	X	X	X	X
Facility admissions	1-3	1		X	X	X
PROMIS Depression	4-12	1-2	X	X	X	X
PROMIS Anxiety	4-12	1-2	X	X	X	X
PROMIS Physical function	4-12	1-2	X	X	X	X
OARS IADL	6	2	X	X	X	X
Falls	1	<1	X	X	X	X
Frailty phenotype: Weight loss	2	<1	X		X	X
Frailty phenotype: Exhaustion	5	2	X		X	X
Frailty phenotype: Activity level	6-18	2-5	X		X	X
Number of medications for polypharmacy	4	1	X			
Race/ethnicity, education, income, demographics	6	2	X			
Total time for Subject reported outcomes			*13-20 minutes*	*7-10 minutes*	*11-17 minutes*	*11-17 minutes*

Race/ethnicity, education, income, demographics

1. What is the highest grade you finished in school?

- 1-8 grades
- 9-11 grades
- High school graduate
- Some post-college work
- Some college
- Junior college degree
- College degree (BA/BS)
- Advanced degree

2. What is your marital status?

- Single, never married

- Married
- Separated
- Divorced
- Widowed

3. What is your current employment status? (please choose all that apply)

- Employed 32 hours a week or more
- Employed less than 32 hours a week
- Full-time student
- Part-time student
- Homemaker
- On medical leave
- Disabled
- Unemployed
- Retired
- Other

4. What is your race? (please select all that apply)

- White
- Asian
- Black or African-American
- Native Hawaiian or Other Pacific Islander
- Native Indian or Alaskan Native
- Don't know

5. What is your ethnicity?

- Hispanic or Latino
- Not Hispanic or Latino
- Don't know

6. Please specify your household gross annual income. Include earnings by all family members living in your household, before taxes.

- Less than $20,000
- $20,000 - $39,999
- $40,000 - $59.999
- $60,000 - $79,999
- $80,000 - $99.999
- $100,000 or more

7. What the zip code of your primary residence?

<u>Number of medications for polypharmacy</u>

1. Are you taking any medications?

- Yes
- No

2. If yes, how many prescribed medications are you taking on a daily basis?

- ___ medications

3. How many over the counter medications are you taking on daily basis?

- ___ medications

4. How many herbs and vitamins are you taking on a daily basis?

- ___ herbs and vitamins

Karnofsky performance status from patient

1. Which of the following phrases best characterizes you at this time? (Please select one response)

- Normal, no complaints, no symptoms of disease
- Able to carry on normal activity, minor symptoms of disease
- Care for self, unable to carry on normal activity or to do active work
- Require occasional assistance but able to care for most of personal needs
- Require considerable assistance for personal care
- Disabled, require special care and assistance
- Severely disabled, require continuous nursing care

OARS IADL

1. Can you use the telephone…

- Without help, including looking up and dialing;
- With some help *(can answer phone or dial operator in an emergency, but need a special phone or help in getting the number or dialing)*; or
- Are you completely unable to use the telephone?

2. Can you get to places out of walking distance…

- Without help *(can travel alone on busses, taxis, or drive your own car)*;
- With some help *(need someone to help you or go with you when traveling)*; or
- Are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation)…

- Without help *(taking care of all shopping needs for yourself, assuming you have transportation)*;
- With some help *(need someone to go with you on all shopping trips)*; or
- Are you completely unable to do any shopping?

4. Can you prepare your own meals…

- without help (*plan and cook full meals yourself*);
- with some help (*can prepare some things but unable to cook full meals yourself*); or
- are you completely unable to prepare any meals?

5. Can you do your housework...

- without help (*can clean floors, etc.*);
- with some help (*can do light housework but need help with heavy work*); or
- are you completely unable to do any housework?

6. Can you take your own medicines…

- Without help *(in the right doses at the right time)*;
- With some help *(able to take medicine if someone prepares it for you and/or reminds you to take it)*; or
- Are you completely unable to take your medicines?

7. Can you handle your own money…

- Without help *(write checks, pay bills, etc.)*;
- With some help *(manage day-to-day buying but need help managing your checkbook and paying your bills)*; or
- Are you completely unable to handle money?

Falls in past 6 months

Question has been modified from text box, to multiple choice response in order to control data entry in electronic format.

1. How many times have you fallen in the last 6 months?

- 0 times
- 1 time
- 2 times
- 3 or more times

Facility admissions

At day 100 and 180

1. Have you been admitted to a skilled nursing facility in the last 3 months? This would include an acute rehabilitation facility, nursing-home, or sub-acute rehabilitation. Do NOT include admissions to the hospital.

- Yes
- No
- unsure

At day 365

1. Have you been admitted to a skilled nursing facility in the last 6 months? This would include an acute rehabilitation facility, nursing-home, or sub-acute rehabilitation. Do NOT include admissions to the hospital.

- Yes
- No
- unsure

Frailty phenotype: Weight loss[*]

Questions have been modified for electronic and paper administration during which patient may not be able to self-weigh or recall exact previous weights. Also modified to remove "Refused" response item, as patients may skip question to refuse.

At Pre-HCT

1. To the best of your knowledge, have you lost or gained weight over the past year?

- Yes
- No
- Don't know

2. [if yes] Did you lose or gain weight because you were trying to, or not (For example, by dieting or exerciseing)?

- Tried to
- Did not try to
- Don't know

Frailty phenotype: Exhaustion[*]

Questions have been modified to remove "Refused" response item, as patients may skip question to refuse.

[*] https://www.johnshopkinssolutions.com/solution/frailty/

[*] https://www.johnshopkinssolutions.com/solution/frailty/

1. In the past month, on average have you been feeling unusually tired during the day?

- Yes
- No
- Don't know

2. If yes, have you been feeling unusually tired:

- All of the time
- Most of the time
- Some of the time
- Don't know

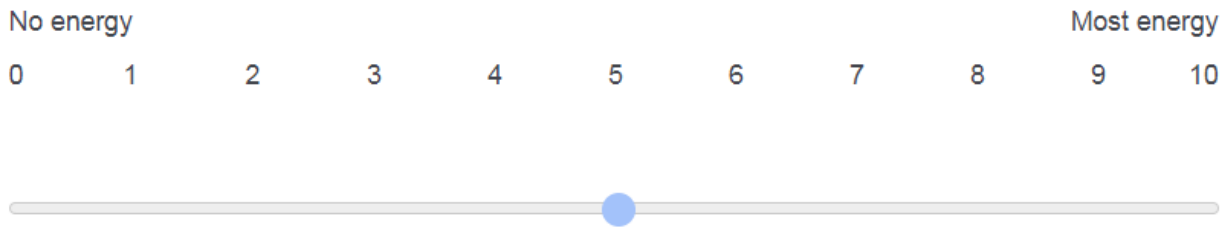
3. In the past month, on average, have you felt unusually weak?

- Yes
- No
- Don't know

4. If yes, have you been feeling weak:

- All of the time
- Most of the time
- Some of the time
- Don't know

5. Using the scale below, would you please rate your usual energy level on a scale from 0 to10 where 0 is no energy and 10 is the most energy that you have ever had. Please give a number between 0 and 10 that describes your usual energy level while awake in the last month?



Frailty phenotype: Activity level*

Questions have been modified for electronic administration and to remove "Refused" response item, as patients may skip question to refuse.

1. During the past two weeks have you walked for exercise?

- Yes
- No

* https://www.johnshopkinssolutions.com/solution/frailty/

- Don’t know

2. If yes, how many times in the past two weeks have you walked for exercise?

- _____ times

3. If yes, what is the average amount of time you spent each time you walked for exercise?

- ___ hours
- ___ minutes

4. During the past two weeks have you done moderately strenuous household chores, like scrubbing and vacuuming?

- Yes
- No
- Don’t know

5. If yes, how many times in the past two weeks have you done moderately strenuous household chores?

- _____ times

6. If yes, what is the average amount of time you spent each time did moderately strenuous household chores?

- ___ hours
- ___ minutes

7. During the past two weeks have you done moderately strenuous outdoor chores, like raking or mowing the lawn, shoveling snow, or working in the garden?

- Yes
- No
- Don’t know

8. If yes, how many times in the past two weeks have you done moderately strenuous outdoor chores?

- _____ times

9. If yes, what is the average amount of time you spent each time you did moderately strenuous outdoor chores?

- ___ hours
- ___ minutes

10. During the past two weeks have you been dancing?

- Yes
- No
- Don’t know

11. If yes, how many times in the past two weeks have you been dancing?

- _____ times

12. If yes, what is the average amount of time you spent each time you have been dancing?

- ___ hours
- ___ minutes

13. During the past two weeks have you been bowling?

- Yes
- No
- Don't know

14. If yes, how many times in the past two weeks have you been bowling?

- _____ times

15. If yes, what is the average amount of time you spent each time you have been bowling?

- ___ hours
- ___ minutes

16. During the past two weeks have you been participated in any regular exercise program, such as stretching or strengthening exercises, swimming or any other regular exercise program?

- Yes
- No
- Don't know

17. If yes, how many times in the past two weeks have you participate in any regular exercise program?

- _____ times

18. If yes, what is the average amount of time you spent each time you have participated in any regular exercise program?

- ___ hours
- ___ minutes

6.4.1 APPENDIX 4.1: PROMIS Item Banks[**]

PROMIS Item Bank v. 1.0 - Emotional Distress – Depression – Calibrated Items

Subjects will respond to between 4 and 12 items from this item bank. Items in gray are included in the short form version of this assessment that is administered on paper.

Please respond to each item by marking one box per row.

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I felt worthless……..	1	2	3	4	5
I felt that I had nothing to look forward to.	1	2	3	4	5
I felt helpless……	1	2	3	4	5
I withdrew from other people……..	1	2	3	4	5
I felt that nothing could cheer me up…	1	2	3	4	5
I felt that I was not as good as other people……..	1	2	3	4	5
I felt sad……	1	2	3	4	5
I felt that I wanted to give up on everything…….	1	2	3	4	5
I felt that I was to blame for things……..	1	2	3	4	5
I felt like a failure…….	1	2	3	4	5
I had trouble feeling close to people……	1	2	3	4	5
I felt disappointed in myself…….	1	2	3	4	5
I felt that I was not needed……..	1	2	3	4	5
I felt lonely……..	1	2	3	4	5
I felt depressed…….	1	2	3	4	5
I had trouble making decisions…….	1	2	3	4	5
I felt discouraged about the future……	1	2	3	4	5
I found that things in my life were overwhelming……..	1	2	3	4	5
I felt unhappy……..	1	2	3	4	5
I felt I had no reason for living…….	1	2	3	4	5
I felt hopeless…….	1	2	3	4	5
I felt ignored by people……..	1	2	3	4	5
I felt upset for no reason……	1	2	3	4	5
I felt that nothing was interesting……..	1	2	3	4	5
I felt pessimistic…….	1	2	3	4	5
I felt that my life was empty……..	1	2	3	4	5
I felt guilty…….	1	2	3	4	5
I felt emotionally exhausted……..	1	2	3	4	5

[**] https://journals.lww.com/lww-medicalcare/Fulltext/2007/05001/Developing_the_Patient_Reported_Outcomes.1.aspx

PROMIS Item Bank v. 1.0 - Emotional Distress – Anxiety – Calibrated Items

Subjects will respond to between 4 and 12 items from this item bank. Items in gray are included in the short form version of this assessment that is administered on paper.

Please respond to each item by marking one box per row.

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I felt fearful	1	2	3	4	5
I felt frightened	1	2	3	4	5
It scared me when I felt nervous	1	2	3	4	5
I felt anxious	1	2	3	4	5
I felt like I needed help for my anxiety	1	2	3	4	5
I was concerned about my mental health ..	1	2	3	4	5
I felt upset	1	2	3	4	5
I had a racing or pounding heart	1	2	3	4	5
I was anxious if my normal routine was disturbed	1	2	3	4	5
I had sudden feelings of panic	1	2	3	4	5
I was easily startled	1	2	3	4	5
I had trouble paying attention	1	2	3	4	5
I avoided public places or activities	1	2	3	4	5
I felt fidgety	1	2	3	4	5
I felt something awful would happen	1	2	3	4	5
I felt worried	1	2	3	4	5
I felt terrified	1	2	3	4	5
I worried about other people's reactions to me	1	2	3	4	5
I found it hard to focus on anything other than my anxiety	1	2	3	4	5
My worries overwhelmed me	1	2	3	4	5
I had twitching or trembling muscles	1	2	3	4	5
I felt nervous	1	2	3	4	5
I felt indecisive	1	2	3	4	5
Many situations made me worry	1	2	3	4	5
I had difficulty sleeping	1	2	3	4	5
I had trouble relaxing	1	2	3	4	5
I felt uneasy	1	2	3	4	5
I felt tense	1	2	3	4	5
I had difficulty calming down	1	2	3	4	5

PROMIS® Item Bank v2.0 – Physical Function

Subjects will respond to between 4 and 12 items from this item bank. Items in gray are included in the short form version of this assessment that is administered on paper.

Please respond to each item by marking one box per row.

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to move a chair from one room to another?	5	4	3	2	1
Are you able to bend down and pick up clothing from the floor?	5	4	3	2	1
Are you able to stand for one hour?	5	4	3	2	1
Are you able to do chores such as vacuuming or yard work?	5	4	3	2	1
Are you able to push open a heavy door? ..	5	4	3	2	1
Are you able to exercise for an hour?	5	4	3	2	1
Are you able to carry a heavy object (over 10 pounds /5 kg)?	5	4	3	2	1
Are you able to stand up from an armless straight chair?	5	4	3	2	1
Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	5	4	3	2	1
Are you able to reach into a high cupboard?	5	4	3	2	1
Are you able to use a hammer to pound a nail?	5	4	3	2	1
Are you able to run or jog for two miles (3 km)?	5	4	3	2	1
Are you able to cut your food using eating utensils?	5	4	3	2	1
Are you able to go up and down stairs at a normal pace?	5	4	3	2	1
Are you able to go for a walk of at least 15 minutes?	5	4	3	2	1
Are you able to run on uneven ground?	5	4	3	2	1
Are you able to open a can with a hand can opener?	5	4	3	2	1
Are you able to pull heavy objects (10 pounds/ 5 kg) towards yourself?	5	4	3	2	1
Are you able to step up and down curbs? ..	5	4	3	2	1
Are you able to get up from the floor from lying on your back without help?	5	4	3	2	1
Are you able to stand with your knees straight?	5	4	3	2	1
Are you able to exercise hard for half an hour?	5	4	3	2	1
Are you able to wash your back?	5	4	3	2	1
Are you able to open and close a zipper? ..	5	4	3	2	1

Are you able to put on and take off a coat or jacket?	5	4	3	2	1
Are you able to stand for short periods of time?	5	4	3	2	1
Are you able to dry your back with a towel?	5	4	3	2	1
Are you able to run at a fast pace for two miles (3 km)?	5	4	3	2	1
Are you able to turn a key in a lock?	5	4	3	2	1
Are you able to squat and get up?	5	4	3	2	1
Are you able to carry a laundry basket up a flight of stairs?	5	4	3	2	1
Are you able to write with a pen or pencil?	4	3	2	1	1
Are you able to put on a shirt or blouse? ...	5	4	3	2	1
Are you able to get out of bed into a chair?	5	4	3	2	1
Are you able to pull on trousers?	5	4	3	2	1
Are you able to peel fruit?	5	4	3	2	1
Are you able to bend or twist your back? .	5	4	3	2	1
Are you able to brush your teeth?	5	4	3	2	1
Are you able to sit on the edge of a bed? .	5	4	3	2	1
Are you able to tie your shoelaces?	5	4	3	2	1
Are you able to run errands and shop?	5	4	3	2	1
Are you able to button your shirt?	5	4	3	2	1
Are you able to wash and dry your body? ..	5	4	3	2	1
Are you able to get in and out of a car?	5	4	3	2	1
Are you able to carry two bags filled with groceries 100 yards (100 m)?	5	4	3	2	1
Are you able to jump up and down?	5	4	3	2	1
Are you able to climb up five steps?	5	4	3	2	1
Are you able to wash dishes, pots, and utensils by hand while standing at a sink? .	5	4	3	2	1
Are you able to make a bed, including spreading and tucking in bed sheets?	5	4	3	2	1
Are you able to carry a shopping bag or briefcase?	5	4	3	2	1
Are you able to take a tub bath?	5	4	3	2	1
Are you able to change the bulb in a table lamp?	3	2	1	1	1
Are you able to press with your index finger (for example ringing a doorbell)? ...	4	3	2	1	1
Are you able to put on and take off your socks?	5	4	3	2	1
Are you able to shave your face or apply makeup?	5	4	3	2	1
Are you able to squeeze a new tube of toothpaste?	4	3	2	1	1
Are you able to cut a piece of paper with scissors?	4	3	2	1	1
Are you able to pick up coins from a table top?	4	3	2	1	1
Are you able to hold a plate full of food?...	5	4	3	2	1

Are you able to pour liquid from a bottle into a glass?	4	3	2	1	1
Are you able to run a short distance, such as to catch a bus?	5	4	3	2	1
Are you able to push open a door after turning the knob?	5	4	3	2	1
Are you able to shampoo your hair?	5	4	3	2	1
Are you able to tie a knot or a bow?.....	5	4	3	2	1
Are you able to lift 10 pounds (5 kg) above your shoulder?	5	4	3	2	1
Are you able to lift a full cup or glass to your mouth?	4	3	2	1	1
Are you able to open a new milk carton? …	5	4	3	2	1
Are you able to open car doors?	4	3	2	1	1
Are you able to stand unsupported for 10 minutes?	5	4	3	2	1
Are you able to remove something from your back pocket?	5	4	3	2	1
Are you able to change a light bulb overhead?	5	4	3	2	1
Are you able to put on a pullover sweater?	5	4	3	2	1
Are you able to turn faucets on and off? ...	4	3	2	1	1
Are you able to reach and get down a 5 pound (2 kg) object from above your head?	5	4	3	2	1
Are you able to stand up on tiptoes?	5	4	3	2	1
Are you able to trim your fingernails?	5	4	3	2	1
Are you able to stand unsupported for 30 minutes?	5	4	3	2	1
Are you able to lift one pound (0.5 kg) to shoulder level without bending your elbow?	5	4	3	2	1
Are you able to walk a block (about 100 m) on flat ground?	5	4	3	2	1
Are you able to run five miles (8 km)?	5	4	3	2	1
Are you able to run 100 yards (100 m)?	5	4	3	2	1
Are you able to run on even ground?	5	4	3	2	1
Are you able to walk up and down two steps?	5	4	3	2	1
Are you able to carry a suitcase up a flight of stairs?	5	4	3	2	1
Are you able to reach into a low cupboard?	5	4	3	2	1
Are you able to climb up 5 flights of stairs?	5	4	3	2	1
Are you able to run ten miles (16 km)?	5	4	3	2	1
Are you able to walk at a normal speed?...	5	4	3	2	1
Are you able to stand without losing your balance for several minutes?	5	4	3	2	1
Are you able to kneel on the floor?	5	4	3	2	1
Are you able to sit down in and stand up from a low, soft couch?	5	4	3	2	1
Are you able to open a tight or new jar? ...	5	4	3	2	1

Are you able to do use your hands, such as for turning faucets, using kitchen gadgets, or sewing?	5	4	3	2	1
Are you able to sit on and get up from the toilet?	5	4	3	2	1
Are you able to transfer from a bed to a chair and back?	5	4	3	2	1
Are you able to be out of bed most of the day?	5	4	3	2	1
Are you able to carry household items, such as heavy boxes or furniture, up a flight of stairs?	5	4	3	2	1
Are you able to water a house plant?	5	4	3	2	1
Are you able to wipe yourself after using the toilet?	5	4	3	2	1
Are you able to turn from side to side in bed	5	4	3	2	1
Are you able to get in and out of bed?	5	4	3	2	1
Are you able to dig a 2-foot (1/2 m) deep hole in the dirt with a shovel?	5	4	3	2	1
Are you able to lift a heavy painting or picture to hang on your wall above eye-level?	5	4	3	2	1
Are you able to paint the walls of a room with a brush or roller for 2 hours without stopping to rest?	5	4	3	2	1
Are you able to row a boat for 30 minutes without stopping to rest?	5	4	3	2	1
Are you able to hand wash and wax a car for 2 hours without stopping to rest?	5	4	3	2	1
Are you able to complete 5 push-ups without stopping?	5	4	3	2	1
Are you able to rake leaves or sweep for an hour without stopping to rest?	5	4	3	2	1
Are you able to do a pull-up?	5	4	3	2	1
Are you able to lift a heavy object (20 lbs/10 kg) above your head?	5	4	3	2	1
Are you able to hit the backboard with a basketball from the free-throw line (13 ft/4 m)?.....	5	4	3	2	1
Are you able to pass a 20-pound (10 kg) turkey or ham to other people at the table?	5	4	3	2	1
Are you able to remove a heavy suitcase (50 lbs/25 kg) from an overhead bin on an airplane or bus?	5	4	3	2	1
Are you able to continuously swing a baseball bat or tennis racket back and forth for 5 minutes?	5	4	3	2	1
Are you able to complete 10 sit-ups without stopping?	5	4	3	2	1
Are you able to climb the stairs of a 10-story building without stopping?.....	5	4	3	2	1

Are you able to walk briskly for 20 minutes without stopping to rest?	5	4	3	2	1
Are you able to come to a complete stop while running?	5	4	3	2	1
Are you able to make sharp turns while running fast?	5	4	3	2	1
Are you able to jump rope for 10 minutes without stopping?	5	4	3	2	1
Are you able to jump over an object that is 1 foot (30 cm) tall?	5	4	3	2	1
Are you able to jump over a puddle that is 3 feet (1 m) wide?	5	4	3	2	1
Are you able to jump 2 feet (60 cm) high?	5	4	3	2	1
Are you able to walk across a balance beam?	5	4	3	2	1
Are you able to stand on one foot with your eyes closed for 30 seconds?	5	4	3	2	1
Are you able to walk in a straight line putting one foot in front of the other (heel to toe) for 5 yards (5 m)?	5	4	3	2	1
Are you able to put your hands flat on the floor with both feet flat on the ground?	5	4	3	2	1
Are you able to carry a large baby (15 lbs/7 kg) out of the house to a car or taxi?	5	4	3	2	1
Are you able to lift and load one 50-pound (25 kg) bag of sand into a car?	5	4	3	2	1
Are you able to climb a 6-foot (2 m) ladder?	5	4	3	2	1
Are you able to push an empty refrigerator forward 1 yard (1 m)?	5	4	3	2	1
Are you able to carry a 50 lb (25 kg) bag of sand 25 yards (25 m)?	5	4	3	2	1
Are you able to pull a sled or a wagon with two children (total 100 lbs/50 kg) for 100 yards (100 m)?	5	4	3	2	1
Are you able to stand up from a push-up position five times quickly?	5	4	3	2	1
Are you able to swim laps for 30 minutes at a moderate pace?.....	5	4	3	2	1
Are you able to dance energetically for an hour?	5	4	3	2	1

	Not at all	Very little	Somewhat	Quite a lot	Cannot do
Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	5	4	3	2	1
Does your health now limit you in exercising regularly?	5	4	3	2	1
Does your health now limit you in bending, kneeling, or stooping?	5	4	3	2	1
Does your health now limit you in doing heavy work around the house like scrubbing floors, or	5	4	3	2	1

lifting or moving heavy furniture?					
Does your health now limit you in lifting or carrying groceries?	5	4	3	2	1
Does your health now limit you in bathing or dressing yourself?	5	4	3	2	1
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?.....	5	4	3	2	1
Does your health now limit you in putting a trash bag outside?	5	4	3	2	1
Does your health now limit you in dancing for half an hour?.....	5	4	3	2	1
Does your health now limit you in hiking a couple of miles (3 km) on uneven surfaces, including hills?	5	4	3	2	1
Does your health now limit you in doing strenuous activities such as backpacking, skiing, playing tennis, bicycling or jogging?	5	4	3	2	1
Does your health now limit you in taking care of your personal needs (dress, comb hair, toilet, eat, bathe)?	5	4	3	2	1
Does your health now limit you in doing moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	5	4	3	2	1
Does your health now limit you in taking part in any sports (swimming, bowling, and so forth)?	5	4	3	2	1
Does your health now limit you in taking a shower?	5	4	3	2	1
Does your health now limit you in going for a short walk (less than 15 minutes)?	5	4	3	2	1
Does your health now limit you in participating in active sports such as swimming, tennis, or basketball?	5	4	3	2	1
Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	5	4	3	2	1
Does your health now limit you in opening a previously opened jar?	5	4	3	2	1
Does your health now limit you in climbing several flights of stairs?	5	4	3	2	1
Does your health now limit you in doing yard work like raking leaves, weeding, or pushing a lawn mower?	5	4	3	2	1
Does your health now limit you in doing two hours of physical labor?	5	4	3	2	1
Does your health now limit you in doing eight hours of physical labor?	5	4	3	2	1
Does your health now limit you in walking more than a mile (1.6 km)?.....	5	4	3	2	1
Does your health now limit you in climbing one flight of stairs?	5	4	3	2	1

Does your health now limit you in getting in and out of the bathtub?.....	5	4	3	2	1
Does your health now limit you in walking about the house?	5	4	3	2	1

	No difficult at all	A little bit of difficulty	Some difficulty	A lot of difficulty	Can't do because of health
How much difficulty do you have doing your daily physical activities, because of your health?	5	4	3	2	1

	Completely	Mostly	Moderately	A little	Not at all
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	5	4	3	2	1

6.5 APPENDIX 5: REFERENCES

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