Title: Maintaining Fitness: Exercise in Patients with Hematologic Malignancy

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1.0 HYPOTHESIS AND OBJECTIVES

1.1 Hypothesis

We hypothesize that it is feasible to recruit patients and implement the Otago Exercise Programme (OEP) safely in patients with hematologic malignancies.
We hypothesize that exercise will improve health related quality of life and decrease functional decline associated with hematologic malignancy.

1.2 Primary Objective

To assess the feasibility of implementing a structured exercise program by evaluating recruitment and retention, exercise program adherence, sustainability, adverse events, and implementation challenges.

1.3 Secondary Objective(s)

To calculate preliminary effect sizes of the impact of an exercise program in patients with hematologic malignancy undergoing therapy, as measured by:

- Cancer and Aging Research Group (CARG) Geriatric Assessment Tool parameters
- Change in Short Physical Performance Battery (SPPB)
- Number and severity of falls
- Hospital readmission rates (if applicable)
- Length of inpatient stays (if applicable)
- Patient Reported Outcome Measurement Information System (PROMIS) for Health related quality of life (HRQL)
- Correlative analysis of peripheral blood biomarkers of aging and inflammation (p16, inflammatory biomarkers, immunosenescence, miRNA)

1.4 Primary Endpoint

The primary end point is feasibility. Feasibility is defined as 80% eligible of participants completing the Otago Exercise Programme (OEP).

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Background of Medical Need

Patients with hematologic malignancy are particularly vulnerable to functional decline due to anemia, resulting in an increased risk of functional dependence, falls, chemotherapy induced-toxicity and mortality.[1] Historically, patients were advised to abstain from physical activity due to chemotherapy-induced immune suppression and fatigue resulting in further physical deconditioning. In recent years, the perspective on physical activity has changed significantly in cancer patients, and many reports document the benefit of exercise in the cancer patient population.[2-4] Physical fitness is highly predictive of survival,[5] yet gauging physical fitness remains a challenge for oncologists and we lack interventions to help this population maintain and/or regain their fitness successfully. Many factors are not modifiable in patients with blood cancer, such as age of diagnosis, genetics of disease, comorbidities, or response to therapy; however exercise is an intervention that can be implemented with a broad range of therapeutic effects. Oncologists require objective assessment of fitness and introducing the physiologic aging biomarker, p16, is potentially practice chap1nging for clinicians to objectively gauge fitness for treatment and/or transplant. This proposal is the first to compare

a biomarker of aging (p16) with baseline physical performance metrics and the first to explore if exercise can improve p16 transcript expression.

Given the serious toll on health status associated with chemotherapy and transplant, the main purpose of this proposal is to conduct a feasibility study to examine predictive measures (SPPB and p16 expression) and preventative measures (OEP) to improve outcomes in patients with hematologic malignancies. Engaging patients in physical activity during therapy is a significant departure from the standard, as patients were previously deemed too ill or too chemotherapy toxic for physical activity intervention. However, with novel therapies and advances in supportive care, our proposed approach to preventing functional decline during transplant is overdue. However, a feasibility study in a single institution is necessary in order to address practical issues in patient recruitment and retention, OEP implementation, and barriers to optimal study delivery and patient safety in this patient population. Here, p16 will be evaluated in the context of a clinical phenotype of fitness, which has not been previously explored. The work accomplished here will inform future multi-study centers to test the effectiveness of the OEP in improving fitness and treatment outcomes (e.g., fall reduction, shorter length of stay during transplant, improvement in quality of life) among hematologic malignancy patients.

2.2 Short Physical Performance Battery (SPPB) and Otago Exercise Programme (OEP)

Prolongation of life is central to cancer care, but the preservation of independent living with functional health is equally important. People who lose functional independence have high rates of morbidity, disability and mortality.[6] Functional decline is amplified in patients with cancer and is a predictor of early death.[7,8] Simple performance tests are powerful predictors of functional decline and can be used for high risk populations. Patients with hematologic malignancy are particularly vulnerable to functional decline due to the protracted process of bone marrow transplant. The SPPB is an objective, validated tool used to capture at risk patients and has been shown to be prognostic in predicting decline in function, re-hospitalization, and mortality.[9] Each 1-unit increase in the SPPB score predicts a 12% reduction in mortality.[5] Functional decline is not an inevitable part of illness or aging, and exercise programs are proven to prevent functional decline, especially in older adults.[6] Older adults who are long-term cancer survivors especially benefit from exercise to reduce functional decline and improve quality of life.[10] The OEP has been found to be an effective exercise regimen to improve functional balance, muscle strength, and prevent fall-related injury and mortality.[11] It has been included successfully in various fall prevention programs, reducing the risk of falls by 30-60%, and was sustainable in 70% of participants after one year.[11]

2.3 Molecular biomarkers are associated with aging, frailty, and physical inactivity

Advances in biomarkers of aging can improve upon subjective measures and better quantify physiologic age. Recently, investigators have refined the ability to quantify biologic age by use of a molecular marker, p16. p16 is a tumor suppressor protein that inhibits cell cycle progression, promotes cellular senescence, and has been associated with frailty phenotypes, physical inactivity, and age related comorbidities.[12] p16, originating from the *INK4/ARF* locus on chromosome 9p21, belongs to a family of cyclin-dependent kinase (CDK) cell cycle inhibitors and prevents cell cycle progression by blocking CDK4/6 dependent phosphorylation of the retinoblastoma tumor suppressor (Rb).[13] Prolonged expression of p16

promotes irreversible cell cycle arrest or cellular senescence. p16 tumor suppressor levels increase exponentially with chronologic aging across most mammalian species including humans.[14,15] Beyond age, p16-induced senescence can be triggered by variety of internal stressors including DNA damage, replication errors, telomere erosion, and reactive oxygen species.[16] External stressors can also trigger p16 expression such as physical inactivity, chemotherapy, and tobacco exposure. Additionally, single nucleotide polymorphisms located near the *INK4/ARF* locus are linked with age-related diseases including cardiovascular disease, diabetes and decreased physical function.[17-19] Therefore, it is believed that p16 levels reflect a physiologic age or fitness. Recently Liu and colleagues demonstrated a means of quantifying this molecular marker of age in peripheral blood T-cells,[20] providing a feasible and relatively non-invasive strategy to monitor p16 expression over time in a clinical setting to predict treatment tolerance and guide clinical decision making. In this research proposal, we focus on the most validated biomarker (p16) however, we are also exploring immunosenescence of aging (T-cell subpopulations, CD28 expression), markers of energy, and epigenetic markers (DNA methylation, miRs). Additional biomarkers of aging and an immunosenescence panel will be collected and explored.

2.4 Falls

Functional decline in the cancer population is multifaceted and complex and is often associated with falls, increased length of stay, and hospital re-admissions.[21] Older adults with hematologic malignancy are especially prone to mobility impairments,[22] and falls are a morbid consequence of functional decline. Falls increase risk of death, among older adults and are the leading cause of fatal and non-fatal injuries.[23] Falls lead to serious complications resulting in some form of injury nearly a third of the time, with serious injury or death reported at rates of 3-8%.[24,25] Risk analyses of patients undergoing bone marrow transplant indicate falls or near-miss episodes in 50-60% of patients analyzed.[26,27] The consequences of a fall in cancer patients results in injury 42% of the time.[25] Thus, malignant hematology patients have much higher rates of adverse consequences compared to the general cancer population.

2.5 Frailty

Frailty is thought to be highly prevalent among older adults and it confers high risk for adverse health outcomes including mortality, institutionalization, falls, and hospitalization.[28,29] It is now defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes. Markers of frailty include age-associated declines in lean body mass, strength, endurance, balance, walking performance, and low activity.[30] Linda Fried, using data from the Cardiovascular Health Study, operationalized a frailty phenotype. She specified that a frailty phenotype was identified by the presence of three or more of the following components: unintentional weight loss of ten or more pounds in the prior year or more than 5% of body weight in the prior year; grip strength in the lowest 20% at baseline, adjusted for gender and body mass index; exhaustion by self-report; slowness, indicated by the slowest 20% of the population, based on time to walk 15 feet, adjusting for gender and standing height; and being among the lowest quintile of physical activity based on a weighted score of kilocalories expended per week. Patients with one or two criteria were considered prefrail. Mortality was six-fold higher for those who met frailty criteria at baseline than that for non-frail for 3-year cumulative survival.[31]

2.6 Goals

The overarching goal of our research is to increase the years of healthy life, with full functional capacity, while undergoing cancer care therapy. Serious health sequela impact recovery during chemotherapy including fatigue, deconditioning and distress; exercise is proven intervention that can positively impact these health outcomes and is underutilized.[32] Given the serious toll on health status associated with cancer treatment, the purpose of this proposal is to conduct a feasibility study to examine predictive and preventative exercise measures to improve outcomes in patients with hematologic malignancies. Engaging patients in physical activity during chemotherapy is a significant departure from the standard, as patients were previously deemed too ill or chemotherapy too toxic for a physical activity intervention. However, with novel therapies and advances in supportive care, our proposed approach to prevent functional decline during transplant is overdue. The OEP fitness program is a means to safely improve fitness levels in a patient population that rarely utilizes exercise as part of the care plan. However, a feasibility study in a single institution is first necessary to address practical issues in patient recruitment and retention as well as OEP implementation, and to address any barriers to optimal study delivery and patient safety in this patient population.

3.0 METHODS

3.1 Patient Selection

Patients will be recruited from the hematology clinics at The Ohio State University. Patients who are undergoing an evaluation for treatment and, or are being treated for a hematologic malignancy are referred by their treating care team for participation in the study. These patients will receive information regarding the proposed study, and will be asked if they would like to undergo screening for their current level of fitness to determine eligibility for study participation. Those agreeing to be screened will sign the study consent and HIPAA forms. They will then undergo the SPPB evaluation. Patients whose total score on the SPPB is ≤ 9, and who meet all other inclusion criteria, will be deemed eligible to continue in the study. Eligible patients who have consented to participate in this study will be assigned a study ID. A peripheral blood sample will also be collected from them for research purposes (See Section 6.0).

Failed screening (i.e. >9 on SPPB) will be captured as part of feasibility. In addition, reasons why patients decline participation will be tracked without documenting patient identifiers [**APPENDIX A**]. For example, patient declined enrollment due to physical activity being judged as too difficult.

3.2 Patient Selection Inclusion Criteria

- Patients with hematologic malignancy receiving care (chemotherapy, immunotherapy, targeted agents, bone marrow transplant, or other) for their hematologic malignancy at the Ohio State University.
- Age $\geq$60 years
- Impairments in physical function, as defined by a score $\leq$9 on the SPPB pre-screen
- Medical clearance from an oncologist or primary care physician stating the participant is able to participate in an unsupervised, moderate-intensity physical activity program
- Ability to understand and the willingness to sign a written informed consent document

3.3 Patient Selection Exclusion Criteria

- Prisoners
- Any medical condition including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness that would limit compliance with study procedures.

3.4 Informed Consent

Discussions between the study coordinators and/or medical oncologists and study participants will occur in clinic. The study coordinators will address all questions regarding the study and consent form and emphasize that the participant can withdraw from the study at any point in time. If patients are interested in participating in the study and meet all eligibility criteria, they will sign the consent form and then be assessed for eligibility and, when applicable, register as detailed below.

3.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.6 Study Procedures

A maximum of 100 patients will be recruited to the exercise protocol. Their participation will be supervised by a designated physical therapist (PT). Participants will meet with the PT at Martha Morehouse for their initial assessment and OEP instruction. The OEP will serve as a structured guide while providing education and motivation. Patients will undergo an initial assessment (short physical performance battery) measuring their strength, balance and gait as well as an individualized OEP based on their physical capacity and health. Patients will receive information on the rationale and benefit of exercise. The PT will ensure that the patient can perform the exercises correctly and safely, making adjustments as needed due to physical limitations such as pain and/or tolerance. The PT will provide home based instructions on exercise, assess patient safety during exercises, assess need for a walking aid, guide patient on appropriate footwear, fall education and exercise compliance, as examples of an OEP evaluation. The PT will monitor the program and provide appropriate advice on exercise progression based on patients' response to exercise. [**APPENDIX B**].

The patient will complete a total of 3 study visits, coordinated with the patients primary oncologist visit. The patient will complete study visit 1 prior to their first physical therapy appointment. The second study visit is at the completion of the OEP and the third study visit is at the end of study (6 months post-visit 1 or post-physical therapy appointment 1, whichever occurred first).These study visits may or may not be in context of a clinical appointment (+/- 30 days)

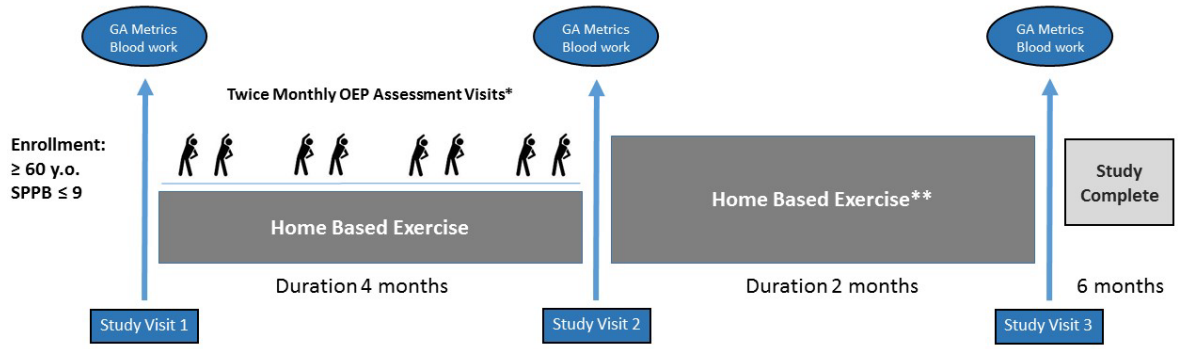
4.0 STUDY DESIGN

4.1 Overview

The PT will assess each patient for individualized physical therapy needs. The PT will design a PT program based upon the individual needs (e.g. weekly, bi-weekly etc). Patients will be instructed on the OEP. The OEP is a combination of physical therapist prescribed exercise and home based exercise recognized to improve balance and functional decline **(Table 1**).[33] The structured OEP focuses on strengthening, balance retraining, and walking. OEP requires minimal training and can be provided by any physical therapist. OEP home-based exercise

requires patient engagement and takes approximately 30 minutes, three times weekly, with walking twice weekly. Participants will record exercise, walking and falls in a weekly diary. The OEP physical therapy portion involves 8 visits over 4 months. All physical therapists engaged in the protocol are OEP certified. Patients will be assessed on their progress with the OEP at their twice monthly appointments. Following these appointments, patients who go on to bone marrow transplant will receive inpatient PT consults a minimum of twice weekly. During these visits, evaluation of strength, balance and walking will be assessed. Before discharge, home based exercises will be reviewed and encouraged. Documentation of physical therapy sessions will be noted and include the level of participation or lack thereof (patient in testing, unwell, declined participation). After the initial 8 physical therapy appointments, patients who will not have a bone marrow transplant will continue with their home-based exercises.

4.2 Study Schema



*Physical therapy appointments are scheduled as standard of care and any additionally necessary physical therapy appointments are arranged as needed at the suggestion of the Physical Therapist. Thus, more than 8 physical therapy visits may be recommended for some patients.
**Transplant patients will receive twice weekly physical therapy in consult during their transplant admission. They will resume home based exercise upon discharge.

4.3 Self-Efficacy in Physical Activity

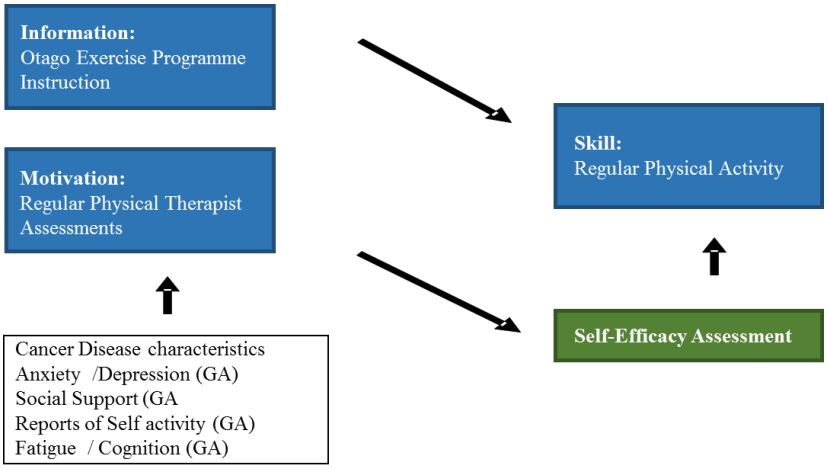
Our intervention is a study of health behavior and is based on a model of health education and promotion through a structured exercise program; Otago Exercise Programme (OEP). We have incorporated major constructs of the self-efficacy[34,35] health behavior theory to better understand the influences of adherence in cancer patients who participate in physical activity.[36] This present research will evaluate the notion that self-efficacy is imperative for performance in sustaining physical activity.[37] We aim to improve physical activity in a population of older adults who are at risk for functional decline and who we believe are motivated by their cancer diagnosis to adhere to physical activity. This model of health promotion is based upon the Information-Motivation-Behavioral (IMB) model[38-40] where we have structured the design, implementation and evaluation of a physical activity program (OEP) based on a health behavior change (i.e. physical activity) that is intended to promote regular exercise and therefore improve quality of life for the participant (Information-Motivation-Behavioral Model and Self Efficacy Schema).

Theories, or ideas that explain behavior, on motivation or behavioral change factors that affect individual physical activity are an active area of investigation.[41] With this background, we have integrated determinants of the individual cancer patient (cancer type, stage, treatment) with a structured environment to promote physical activity. We aim to study the importance of motivation, physical ability, and opportunity as mediators of physical activity.

Motivation will be analyzed via a questionnaire based upon the theory of reasoned action and behavior,[42] where we examine the relationship of belief, attitudes, intentions and behavior at baseline.[43] We will therefore examine by validated tools the attitudes toward physical activity, subjective norms, and perceived behavioral norm **[Appendix C]**. Our IMB model focuses on self-efficacy, imperative for home based exercise, in which the participant must develop skills and confidence in one's own ability. Self-efficacy is based upon the social cognitive theory in which the action of physical activity is more likely when the participant is confident in their ability resulting in sustained behavior. We will assess self-efficacy using a baseline 15-item instrument (Garcia & King, 1991) where items are rated on a 0%-100% scale (e.g., I could walk when tired, I could walk when my schedule is hectic) (0% = Cannot do it at all, 100% = Certain that I can do it) (Cronbach's α pre = .95) **[Appendix D]**. These theories have helped guide our infrastructure in developing a structured exercise program to induce behavior change (i.e. physical activity). Therefore, we will include a self-efficacy validated scale that will be incorporated at baseline and also during monthly physical therapy assessments with the physical therapist **(Table 2).** The Clinical Research Coordinator (CRC) will gather exercise logs and administer the self-efficacy validated tools; we will explore barriers to exercise using both open-ended and direct questions **[Appendix E]**. The CRC will discuss any discordance in reported physical activity and barriers of physical activity (i.e. are you having any problems with exercising at home?). These open ended questions will be captured and recorded.

We have identified that patients with hematologic malignancy are vulnerable to functional decline due to anemia, resulting in an increased risk of functional dependence, falls, chemotherapy induced-toxicity and mortality[1]. The benefit of physical activity in patients is well established however behavioral and environmental factors are barriers to activity and structured interventions to improve upon physical activity are lacking.[2-4] We have applied this model by identifying the factors that influence motivation using Geriatric Assessment (GA) tools, where we examine many aspects of health that influence disease outcomes and health behaviors such as: social support, baseline physical activity, cognition, anxiety, depression, fatigue. The social assessment is influenced by the health, behavior and environment that is also being collected (i.e. distance to OSU cancer center, cancer type, stage of disease, chemotherapy treatment). Educational factors contribute to baseline health behavior and these factors will also be captured. Finally the OEP program is a validated educational strategy to promote healthy functional activity. The second portion of our theory analysis is based upon feasibility that we can implement and evaluate the process of a structured exercise program within the cancer center program. We aim to also evaluate the impact of the exercise program via patient reported outcomes. In conclusion, as a secondary analysis, we aim to calculate preliminary effect sizes based upon change of Geriatric Assessment score parameters, change in Short Physical Performance Battery (SPPB) scores, number and severity of falls, hospital readmission rates, length of inpatient stays and change in Patient Reported Outcome Measurement Information System (PROMIS) for Health related quality of life (HRQL) scores. This planning model of a structured exercise program is schematically represented below.

4.4 Information-Motivation-Behavioral Model and Self Efficacy Schema



4.5 Study Measures

4.5.1 Short Physical Performance Battery (SPPB)

At the time of screening patients will undergo a SPPB [**APPENDIX F**]; patients with a SPPB score of $\leq$9 will be allowed to enroll in the study. Patients will complete an SPPB at the completion of the OEP and at 6 months (3 times total). This test will be administered by the Clinical Research Coordinator and scores will be captured. The SPPB is a validated tool composed of a simple battery of objective physical performance tests that involve gait speed, balance and ability to rise from a chair. The SPPB was designed to evaluate balance, gait, strength, and endurance initially in a cohort of 5000 community-dwelling seniors. The tool can be administered in approximately 10 minutes. The SPPB can predict mortality and nursing home admissions among older adults. Interestingly, the measure can also detect a gradient of risk for mortality and nursing home admission among older adults with no current disability.[9] It also has been shown to predict mortality in cancer survivors.[5] The tool assesses balance through use of the side-by-side stand, semi-tandem stand, and tandem stand; strength is assessed with the chair stand test and repeated chair stands; and gait speed is evaluated through use of an 8-foot walk test. Scores are assigned for each of the tests and an aggregate score is assigned ranging from 0-12, with higher scores indicating greater physical function. SPPB scores are classified into 4 categories: very low physical function (0-3); low physical function (4-6); moderate physical function (7-9) and high physical function (10-12). An alpha internal consistency of 0.76 has been reported.[9] The SPPB will be performed twice while the patient is on study, once as a pre-screen enrollment and a second SPPB at completion of the structured exercise program.

4.5.2 Geriatric Assessment Tools (GA)

At the time of screening patients will undergo a GA [**APPENDIX G**]. The GA will be repeated at the completed of the OEP and at 6 months (3 times total). This test is self-administered survey with the aid of a CRC; scores for the GA will be captured.

Geriatric assessments are performed in a traditional geriatric population to identify current health problems and guide interventions to reduce adverse outcomes and optimize the functional status of elderly patients. In an oncology setting, it may be useful to identify occult geriatric syndromes and provide interventions that can improve the ability of patients

to undergo treatment for their cancer. The typical domains of a comprehensive geriatric assessment (GA) include evaluations of functional status, comorbid medical conditions, cognitive status, psychological state, falls, social support, nutritional status, and a review of the medication list.

A geriatric assessment is utilized to capture information about a patient's medical history as well as functional, cognitive, and psychosocial status, which can then be used by treating physicians to identify the most vulnerable patients (for example, those at high risk for chemotherapy toxicity). However, these assessments have not been routinely used in oncology practice because of the time and resources required for their administration. A geriatric assessment tool (that can be completed primarily by patients) was developed for incorporation into oncology clinical trials and routine care settings.[44,45] As an example, among older adults with newly diagnosed AML, overall survival was found to be significantly shorter for patients who screened positive for objectively measured impairment in mobility and cognition providing conclusive evidence that a comprehensive assessment tool can at least improve risk stratification for patients undergoing intensive therapy.[46] Furthermore, geriatric assessments can predict survival and toxicities in older adults with multiple myeloma.[47] Barriers to incorporate geriatric assessments into routine clinical care include lack of infrastructure to support these assessments and how to utilize the data to make treatment decisions.
A clinical research coordinator will be trained to administer the Cancer and Aging Research Group's geriatric assessment (CARG GA) and healthcare provider assessments. Training for the geriatric assessment is available through the CALGB geriatric assessment instrument training website:

https://www.allianceforclinicaltrialsinoncology.org/training/auth/1%3A1%3A0%3A0%3A0/

A copy of the GA results may be made available to the patient's primary oncologist. Medical records may also be reviewed to determine if any actions were performed by the primary oncologist, as a result of the GA information (e.g.: a patient was identified to have nutritional concerns and on a subsequent visit a nutritionist was consulted).

4.5.3 PROMIS: Patient-Reported Outcome Measurement Information System Global Health Scale Short Form v1.1 HRQL measures provide invaluable information to the clinician regarding the patient experience of treatment or intervention. Large population based studies have demonstrated that patients with hematologic malignancy report some of the poorest HRQL.[48] However, exercise is reported to improve HRQL in cancer patients undergoing active treatment.[49] The PROMIS Global Health Scale has been rigorously tested for reliability and validity and can be applied to all populations.[50] It consists of 10 questions and will be self-administered to patients monthly. [**APPENDIX H**]

4.5.4 Falls
Falls in patients receiving chemotherapy are associated with a 3-fold greater risk of mortality.[51] Fall and fall severity will be captured as self-report of calendar recorded falls, where patients denote on the calendar day when they had a fall associated with commentary on the event (e.g. fall with abrasion). Calendar recorded events is a valid method of self-reporting fall events and is shown to be more accurate than short term recall in patients with falls.[52] Falls will be captured twice monthly. Research coordinators may contact the patient

by phone if a fall has occurred to identify the severity of the fall and/or injuries [**APPENDIX I**].
Inpatient admission falls will be captured per institution guidelines, as all falls are required to be reported to the Quality and Patient Safety Department. Specific information regarding patients enrolled in both as an Exercise Participant and Survey Participant will be gathered. Hospital Injury Level and the National Database of Nursing Quality Indicators (NDNQI) injury level will be captured.

4.5.5 Exercise Intervention: Otago Exercise Programme (OEP)

Exercise interventions are an established method of improving physiologic and functional performance in older adults. The structured OEP focuses on strengthening, balance retraining, and walking. OEP requires minimal training and can be provided by any physical therapist. OEP requires patient engagement and takes approximately 30 minutes three times weekly, with walking twice weekly. All physical therapist engaged in the protocol are OEP certified. The OEP is 8 physical therapy visits over 4 months. Participants will record daily of walking, exercise and falls in an exercise journal [**APPENDIX J**].

Patients may require more than 2 sessions monthly of physical therapy according to the physical therapist prescribed recommendations. In this event, exercise logs and fall diaries will be collected at their 1st and 3rd visit monthly. Patients will be reimbursed for their travel at these two visit times only (see Section 5.8).

Table 1. Otago Exercise Programme (OEP)

	Strengthening	Balance Retraining	Walking
Assessment	30 Second Chair Stand Test	Four-Stage balance Test	Timed Up and Go
Activity	Five leg muscle strengthening exercises Four levels of difficulty	Twelve balance retraining exercises Four levels of difficulty	Advice about walking
Intensity	Moderate Challenge 8-10 repetitions before fatigue	Moderate Challenge Each exercise at a level the patient can safely perform	Usual pace with usual walking aid
Progressions	Increases from one to two sets Increase amount of ankle weight after 2 sets of 10	Supported exercise and unsupported exercise	Walk indoors Advance to walking outdoors when strength and balance have improved
Length of Exercise Sessions	Approximately 30 minutes total for exercises; Exercises can be divided up over the day		30 minutes; can be split into three 10 minute walks throughout the day
Home Based Frequency	3 times a week	At least 3 times a week	Twice a week
Duration	Physical therapy (8 visits, twice monthly, until transplant or 4 months) Transplant physical therapy consult (twice weekly physical therapy consult during transplant admission). Home based exercise throughout their 6 month enrollment.		

4.5.6 OEP Evaluation

At the completion of the OEP, patients will be asked to indicate their likes and dislikes about the program, any logistical challenges, how worthwhile the program was to them personally, and ways in which the implementation of the program could be improved. Records will be kept of any patient adverse events during the course of the OEP [**APPENDIX K**].

4.5.7 Blessed Orientation-Memory-Concentration Test (BOMC)

The BOMC [**APPENDIX L**] is a widely used screening test for dementia and evaluation of orientation, registration, and attention. The test allows providers and caregivers to screen for suspected dementia in older patients. It was originally validated on older patients living in both skilled nursing facilities and community-dwelling. The BMOC is a weighted 6-item instrument and takes less than 10 minutes to complete. Scores range from 0-28, and scores greater than 10 are consistent with dementia.

Table 2. Study Measures

	Study Visit 1: Baseline	Study Visit 2: Completion of OEP*	Study Visit 3: 6 months*
CARG GA	X	X	X
SPPB	X	X	X
PROMIS[a]	X	X	X
Falls[b]	X	X	X
OEP Evaluation		X	
Physical Therapy Adherence[c]		X	X
Biomarker[d]	X	X	X
Motivation	X		
Self-Efficacy	X	X	X
Barriers	X	X	X
Blessed[e]	X*	X*	X*
*(+/-)30 days; administered monthly; biomarkers (+/-) 14 days			

a. PROMIS measures are captured monthly from the time of OEP enrollment (maximum 6 surveys)

b. Falls are captured twice monthly from the time of OEP enrollment via self-report calendar; inpatient falls are captured during hospitalization and are not a self-report.

c. Physical therapy adherence will be captured by the number of visits (inpatient and outpatient) and if patient is achieving the standard based upon the physical therapist assessment (1-achieving the standard, 2-progressing toward the standard, 3-limited progress or not meeting the standard)

d. Blood work will be collected during the study visit with the patients' outpatient hematologist. Attempts will be made to collect blood work during the routine draw, however this is not mandated. Biomarker collection (+/-) 14 days within study visit.

e. If not administered prior to patient's enrollment, the Blessed test will be administered one time at a point after the patient's enrollment in the study.

4.6 Potential Risks

We anticipate that this study will entail minimal physical and psychological risks for study participants. Informed consent will be obtained from all participants prior to study

enrollment. There is a small risk to participants of sustaining an injury while participating in the exercise intervention. Prior to participating in the intervention, all participants must have documentation from their primary oncologist or primary care physician stating that they are capable of participating in a moderate-intensity exercise intervention. There is a small risk of psychological distress associated with completion of the questionnaires. If this occurs, study staff will speak to the participant about the difficulties that the questionnaires have caused and will offer a referral to a mental health professional if necessary.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 Registration Process

- Potential patient identified
- Patient signs informed consent and HIPAA form
- Eligibility Screening
- Worksheet documentation note by the primary oncologist giving the patient medical clearance to participate in physical therapy
- Provide patient with Enrollment Handbook [**APPENDIX M**]
- Register the patient on the study (Oncore)
- Assign a patient study number
- Pend blood work orders
- Documentation of Consent in EPIC
- Schedule twice monthly physical therapy sessions for next 4 months

5.2 Electronic Data Capture

5.2.1 iPAD Survey Administration: Many of the assessments are self-administered (CARG GA, PROMIS, Motivation, Self-efficacy and OEP evaluation) and, when possible, will be administered electronically. Some portions of the survey questionnaires are administered by a research coordinator (portions of the Barriers survey and CARG GA). Electronic administration will be done via an iPad. The questionnaires will be given within the context of routine clinical care. Patients will be provided with an iPad to complete the self-administered surveys. The clinical research coordinator administers the functional and cognitive assessments. The feasibility of an iPad to electronically capture functional assessments requires additional information to determine practicality in an oncology setting. Patients unable to use an iPad or prefer not to use an iPad will have a paper survey options. Data on paper survey preference will be captured. Patients who choose to participate but then discontinue enrollment due to iPad use will be tabulated. In addition, the iPad questionnaire is a timed session and will be compared to published data for each questionnaire/battery to determine efficiency. Furthermore, data capture is complete; questionnaires were designed so one could not advance to the next question without a response including the option “I choose not to answer” for select sensitive questions.

5.2.2 Survey Software and Data Management: All data obtained via the iPad survey platform is supported by Qualtrics, a secure password protected online service. OSU Purchasing has contracted with Qualtrics to provide a single contract and OSU-managed single sign on to the cloud service for provisioning surveys for research at the university.

Qualtrics is the preferred survey tool at OSU and the only tool on contract. Information regarding Data Safety is linked here:

http://fisher.osu.edu/offices/technology/services/support-services/qualtrics

Patients will be enrolled into the Qualtrics survey platform system with a unique identifier code given to them during the registration process in OnCore. The unique identifier code linked to patient identification will be kept in REDCap. All protected health information will be kept in REDCap. REDCap is an electronic data collection (EDC) tool supported by the CCTS. It is a secure, web-based application designed exclusively to support data capture for research studies. Clinical data, and patient diaries will be captured in REDCap.

5.3 Baseline Demographic Questionnaire
Information will be collected on patient demographic information collected via a standard questionnaire administered at baseline and from IHIS

5.4 Clinical data to be obtained
Clinical follow-up for patients with hematologic malignancy will be performed according to the standard institutional guidelines. Clinical data regarding specifics of hematologic malignancy will be obtained from IHIS including but not limited to, diagnosis, date of diagnosis, stage, cytogenetics, prognostic information, treatment history, medications, physical exam parameters, hospitalizations, hospitalization length of stay, rehabilitation needs, bone marrow transplant length of stay, readmissions, transplant outcomes, hematologic and chemistry parameters e.g. CR, LDH, β2-microglobulin.

Patients will be required to complete a follow up geriatric tool assessment at completion of the OEP, this may or may not be in context of a clinical appointment (+/- 30 days).

The following data will be collected from participants at baseline (Study Visit 1), post-OEP (Study Visit 2) and 6 month visits (Study Visit 3), and/or on a monthly basis

- Clinical Information
- CARG GA
- SPPB
- PROMIS HRQL
- Self- Efficacy Questionnaire
- Barriers
- Adverse events
- Motivation *(study visit 1 only)*
- OEP Evaluation *(study visit 2 only)*
- Physical Therapy Tracker **[APPENDIX N]** *(every other physical therapy appointment)*
- Physical Therapy Progress Tracking *(study visit 2 and 3 only)*

The following data will be collected from participants twice monthly at OEP appointments

- Walking, Exercise and Fall Diary

5.5 Adverse Events

Individuals will be asked about exercise-related adverse events at the time of study visit. Any exercise-related injuries will be reported to Dr. Rosko (Principal Investigator). Any reported events will be evaluated for the likelihood that they occurred as a result of exercise. An adverse event is considered serious if it results in any of the following outcomes: 1.) death; 2.) a life-threatening event; 3.) inpatient hospitalization or prolongation of an existing hospitalization >24 hours; 4.) persistent or significant incapacitation or substantial disruption to the participants ability to conduct normal life functions; 5.) congenital anomaly/birth defect; 6.) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon medical judgement, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Serious adverse events related to exercise experienced by patients in this protocol will be reported to the OSU CCC Clinical Trials Office and the Cancer Institutional Review Board (IRB). Information reported will include the number of patients affected, number of patients treated, summary of all adverse events reported to date using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading, a specific list of adverse events requiring expedited reporting to include all serious adverse events [SAEs], and, on an annual basis or as it arises, significant literature reporting developments that may affect the safety of participants or the ethics of the study. Data safety and monitoring activities for each study will continue until all patients have completed their intervention and all patients are beyond the time point at which study-related adverse events would likely be encountered.

5.6 Duration of follow-up

Patients will be followed for approximately 6 months at The Ohio State University Wexner Medical Center.

5.7 Criteria for removal from study

Patients will be removed from the study by patient preference or MD request otherwise will remain on study for 6 months.

5.8 Travel Re-imbursement

Patients who elect to become vendors [**APPENDIX O**] of The Ohio State University will be paid $25 (a maximum of twice monthly) for each physical therapy visit at a total of $200, if they complete all 8 visits. Payment will be given in cash at the time of the physical therapy visit. If patients are scheduled for additional physical therapy sessions, as prescribed by their physical therapist in accordance with routine care, patients will be reimbursed at only one physical therapy appointment, per week, every other week of the month.

6.0 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is feasibility, defined by 80% of eligible participants completing the Otago Exercise Programme (OEP). Program completion is the primary indicator of this feasibility pilot project. 80% completion was chosen based upon the Otago Exercise Programme controlled trials, where the effectiveness of home based exercise to reduce falls in injuries in elderly adults in the community had a 90% completion rate of the trial.[53] When the Otago Exercise Programme was delivered in different centers 87% of participants

completed the trial[54] . When the Otago Exercise Programme was introduced into the primary care practice, older adults (>80) approximately 47% participation occurred and 79% completed one year assessments 55. Therefore, 80% completion was chosen as the feasibility endpoint to achieve the desired effects of improving strength and balance via OEP.

We will describe the proportion of screened patients who agree to participate, the proportion of patients who attend certain percentage of assigned PT sessions and the proportion of patients who complete the whole study along with respective 95% confidence intervals. Study implementation and challenges will be evaluated by patient exercise logs. Exercise levels at home will also be assessed by exercise diary log. Adverse events (AE) and their severity will be captured according to the CTCAE v4.0, and whether any AEs can be attributed to exercise.

6.2 Secondary Endpoint(s)

For the entire cohort of patients, we will describe CARG GA, number of falls, SPPB, PROMIS HRQL scores at all three time points when the relevant data are collected: baseline, after OEP completion and 6 months. Descriptive statistics of these measurements will be provided as well as graphs in order to help visualize the change over time. The proportion of patients who achieve meaningful change in these scores will be described with 95% CI. Difference from baseline will be tested with Wilcoxon signed rank test or McNemar's test for continuous or categorical variables respectively. Take SPPB for example, with 30 patients a two-sided Wilcoxon signed rank test for paired observations will have at least 80% power to detect a medium effect size of 0.55 (i.e. 0.55 standard deviations) for the differences in scores before and after the OEP. Depending on patient retention rate and completeness of the collected data, linear mixed models with repeated measures might be fitted to quantitatively model the changes, but the modeling analysis will mostly be exploratory due to limited sample size. The correlation between these scores including their baseline values and changes over time and other clinical factors of interest such as age, BMI and performance status will also be evaluated.

For patients undergoing transplant, we will describe the following clinical points of interest: inpatient falls, 90-day hospital readmission rate, and length of inpatient stays. Pre and post OEP changes in CARG GA, SPPB and PROMIS HRQL scores and their potential association with these clinical endpoints will be explored graphically.

Findings will largely be exploratory and will need to be validated in larger subsequent multi-center trial.

6.3 Correlative Analysis

Presence of deleterious genes and p16 pre-OEP and post-OEP will be correlated with clinical factors (age, performance status, adherence to OEP), GA profiles, SPPB scores.

Serum studies evaluating mRNA will be characterized and analyzed in relation to functional assessment outcomes as well as clinical outcomes of interest. microRNA measures will be assessed in relation to cytokine measures using graphical analyses and measures of correlation. FDR corrections will be utilized to correct for the simultaneous comparisons of the multiple markers.

Quantified p16 expression pre and post OEP will be described, and independently analyzed in relationship to functional assessment outcomes such as GA scales, SPPB Scores as well as

clinical outcomes of interest (age). In addition, p16 expression will be evaluated in relation to clinical outcomes, such as tolerance of OEP, adherence of OEP, length of hospitalization and readmissions in a descriptive manner. Generalized linear models will be used similar to those described above to assess the impact of p16 expression on GA scores depending on data completeness. Spearman rank correlation coefficients will be used in relation to continuous measures (e.g. age), two-sample tests (Wilcoxon rank sum tests) will be used for comparing p16 expression between two groups (e.g. incidence of del17), and Kruskal-Wallis tests will be used to compare p16 expression between more than two groups. Descriptive statistics and graphical analyses will be used to evaluate p16 expression within each of the groups to better understand potential trends of interest.

7.0 CORRELATIVE ANALYSIS / SPECIAL STUDIES

7.1 Overview

Peripheral blood will be obtained for mRNA, miRNA, and flow cytometry analysis. While specific details of the processing, extraction, and analysis are included in this protocol, these details may change with innovations in laboratory techniques and hence are considered general guidelines only.

7.2 p16 Aging Biomarker: Identifying candidacy for treatment or transplant is generally subjective and is dependent on age, performance status, and comorbidities. The clinical need for objective quantitative measures of physiologic fitness remains unmet. As such, *p16,* a marker of cellular senescence, represents an attractive proxy for physiologic age and may be an additional tool in the clinical evaluation. Many investigations are focusing on biomarkers of age to weigh treatment options and gauge toxicity.[56] We aim to capture physiologic fitness and with use of *p16* expression in peripheral blood T-lymphocytes (PBTL). The molecular biomarker, $p16^{INK4a}$ *(p16)* is an established marker of systemic cellular senescence associated with physiologic aging. *p16* expression increases ~16-fold over an individual's lifetime and can be readily measured in PBTL.[57]

7.3 Correlative Analysis Procedures: Patients enrolled have peripheral blood collected for p16 analysis serially at three time points 1) pre-OEP 2) post-OEP and 3) 6 months. Peripheral blood will be obtained in EDTA coated tubes (10 ml) where CD3+ T-cells will be isolated using RosetteSep Reagents. RNA will be extracted using RNeasy Plus Mini Kit (Qiagen), and analyzed using reverse-transcription real-time quantitative PCR for p16, ARF, and standard housekeeping genes. *p16* mRNA expression will be compared to an age-matched control dataset. The source of this dataset is a primary analysis study previously conducted by the PI, Dr. Ashely Rosko (IRB protocol number 2014C0008). The only information retrieved from this control dataset will be age; no protected health information will be collected. The full dataset has been de-identified and the study team does not have access to identifiable information about this population.

7.4 Feasibility Preliminary Data: Recently, investigators have evaluated the impact of lifestyle on PBTL *p16* expression in healthy volunteers.[58] The authors reported that modifiable factors such as exercise, smoking, and body mass have an age-independent impact on *p16* expression where physical exercise duration showed an inverse association with the level of *p16* T-cell mRNA expression (r^2=0.1922, p<0.0001). This suggests that exercise may

exert protective effects in age-dependent accumulation of senescent cells. External factors such as chemotherapy also impact *p16* expression. In preliminary data, we identified that BMT also significantly increases the expression of T-cell *p16* mRNA expression in patients with multiple myeloma pre- and post-transplant (90 day)**.** As such, we aim to explore if exercise alters p16 expression.

7.5 Obtaining samples

Peripheral blood will be obtained by clinic staff for mRNA, miRNA, and cytokine studies. Samples will be obtained in clinical space (currently on HTC and 5th floor James, as examples).

Specifically, approximately 30ml of peripheral blood will be collected into phlebotomy tubes: up to 10ml in purple top EDTA tubes and 20ml in serum separator tubes.

7.6 Sample processing

Sample pick up and processing will be performed in the Leukemia Tissue Bank using the following general procedure for cryopreservation of serum and plasma.

To obtain the plasma the blood collected in EDTA coated tubes will be transferred to 50 ml sterile tube and centrifuged at 1800 rpm for 10min at room temperature. The supernatant (plasma) will be collected and stored at -80°C for further studies. The cellular pellet will be gently re-suspended in PBS to reach 2X the original volume (for 10ml of plasma 20ml PBS) and then stratified in 1X of Ficoll-Paque. This will be centrifuged at room temperature for 20 min at 2000 rpm. The white ring containing monocytes, T- and B- lymphocytes will be removed and washed with FBS enriched culture media. The tube will be centrifuged at 1200 rpm at room temperature for 6 min. The cellular pellet will be resuspended in 90% FBS and 10% DMSO and placed in cryo-tubes at -80°C and after 3 days will be placed in liquid nitrogen for long-term storage.

For the serum collection the tubes will be centrifuged at 2,200-2,500 rpm for 15 min and the serum will be stored at -80°C.

To obtain T cells: Whole blood collected in a purple top EDTA tube will be divided into two equal volume portions, approximately 5mL each. RosetteSep Human T Cell Enrichment Cocktail (Stem Cell Technologies # 15061) will be added to each tube at a ratio of 50uL per mL of whole blood. Tubes will be mixed by inversion and incubated for 20 minutes at room temperature. Next, samples will be diluted in an equal volume of phosphate buffered saline containing 2% fetal bovine serum (PBS/2%FBS). Diluted samples will be gently mixed and then carefully layered on top of Histopaque 1077 density medium (Sigma-Aldrich #10771) in a 50mL conical tube. The amount of density medium used will equal the original blood aliquot volume (~5mL). Tubes will then be centrifuged at 1200xg for 20 minutes at room temperature with the centrifuge brake set to 'off'. Following separation, enriched T-cells will be removed from the plasma interface using a pipette and placed into a fresh 15mL conical tube. The cells will be washed by adding PBS/2%FBS to the tubes until they are filled to the top fill line. Tubes will then be centrifuged at 400 x g for 4 minutes at room temperature with maximum brake. The resulting supernatant will be removed with a pipette and transferred to a 1.5 mL microcentrifuge tube. This sample will be centrifuged at 400 x g for 4 minutes at room temperature with maximum brake. The resulting supernatant will be carefully and completely removed using a pipette. The remaining T-cell pellet will be stored in a -80 ° freezer until processing.

7.7 RNA recovery and basic analysis of mRNA and miRNA

Analysis of samples will start in the laboratory of Dr. Christin Burd, although this is subject to change. As described below, the Nucleic Acid Shared Resource (section 6.3.1) and occasional proprietary analysis by companies such as RayBioTech (section 6.4) may also be involved. For total RNA extraction from plasma/serum, 3-5ml of sample will be processed using the mirVana Paris kit (Ambion) following the manufacturer's instructions. To increase the RNA recovery and the RNA quality from serum, 1µg of RNA carrier (#4382878, Ambion) will be added to the total volume to allow both a better miRNA recovery and an increased RNA quality from serum samples.

For total RNA extraction from T-cells, cell pellets will be processed using the RNeasy Plus Mini Kit (Qiagen #74134) following the manufacturer's instructions.The concentration and quality of all RNAs will be assessed using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). If the 260/280 ratio is not between 1.70 and 2.30 the RNA sample will be subjected to an extra purification passage. The samples will be submitted to the Nucleic Acid Shared Resource of The Ohio State University for further processing by the NanoString nCounter system for mRNA and miRNA characterization (NanoString, Seattle, Washington, USA).

7.8 p16 mRNA Isolation and Analysis

Under the supervision of Dr. Burd, harvested T-cell mRNA will be converted to cDNA using the Promega ImProm-II Reverse Transcription System (Promega #A3802) and random hexamer primers (Invitrogen #588875) as directed by the manufacturers. p16 levels will be measured using a Taqman-based quantitative RT-PCR methods essentially as described by Liu et al. (20). Validated Taqman-based controls for T-cell purity (CD3G, Applied Biosystems #4331182 Hs00962186), sample viability (p14ARF, Applied Biosystems #4351370 HUMP14-ARF3) and RNA quantity (YWHAZ, Applied Biosystems #4331182 Hs03044281) are included in this analysis. Data clean up: Data will be filtered to exclude relatively invariant features (IQR = 0.5) and features below the detection threshold (defined for each sample by a cutoff corresponding to approximately twice standard deviation of negative control probes plus the mean of them) in at least half of the samples. Basic analysis Using R/Bioconductor and the filtered dataset, linear models for microarray data analysis[59] (Smyth et al., 2005) will be employed with a contrast matrix for the comparisons. P values will be used to rank miRNAs and mRNA of interest, and correction for multiple comparisons will be done by the Benjamini-Hocheberg method[60] (Benjamini et al., 1995). Raw data that is above background, as well as the corresponding quantile-normalized data, will be imported into MultiExperiment Viewer[61] (Saeed et al., 2006; Pichiorri et al. 2013).

7.9 Bone marrow analysis

Some bone marrow aspirates will be obtained as standard of care and analyzed by surgical pathology, cytogenetics, and flow cytometry and this data may be analyzed and incorporated into statistical model building.

8.0 STUDY CALENDAR

Table 3. Study Visit Assessments			
	Study Visit 1: Baseline* (+/- 45 days)	Study Visit 2: POST-OEP Evaluation *(+/- 45 days)	Study Visit 3: 6 Month Follow up *(+/- 45 days)
Signed Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Registration additions	X		
History and Physical	X	X	X
Weight and Height[a]	X	X	X
Adverse Events[b]	X	X	X
KPS	X	X	X
Vitals	X	X	X
CBC with differential[c]	X	X	X
Serum Chemistry and LFT's[d]	X	X	X
Hematologic Cancer Specific Labs[e]	X	X	X
β2 microglobulin, LDH, CRP	X	X	X
Peripheral blood for biomarker analysis[f]	X	X	X

a. Weight to be measured in the same fashion at each time point (with or without shoes, street clothes vs. gown, etc). Height does not need to be repeated after the screening visit.
b. Adverse events (AE) and their severity will be captured according to the CTCAE v4.0 and whether any AEs can be attributed to exercise (physical therapist administered or home based).
c. CBCs will be performed to include at least WBC, hemoglobin, platelets, and absolute neutrophil count.
d. Serum chemistry (electrolytes, BUN, creatinine) and Liver function tests to include transaminases and albumin
e. Myeloma: measure clinically relevant proteins that have previously been abnormal in that patient to include more than one of the following: a) serum immunoglobulins by nephelometry, b) serum & urine protein electrophoresis and immunofixation, c) serum free light chains; and d) 24hr urine total protein (as necessary); NHL: LDH; AML/ALL: % circulating blasts
f. Blood samples (30 mL of blood) will be cryopreserved for correlative analyses (RNA studies, flow cytometry etc.)
* Survey participant data will be captured as part of routine care

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