11. Research Strategy

11. A. Significance

Cancer in the elderly is a growing health care problem. The increased incidence of cancer associated with age, coupled with the projected explosion of the geriatric population, will dramatically increase the burden of cancer in the elderly in the United States[9]. Caring for older adults with cancer requires substantial health care resources, making this a key public health issue[10]. Older adults have been underrepresented in clinical trials, resulting in significant gaps in evidence regarding the risks and benefits of standard therapies[11-13].

Cancer treatment may contribute to short- and long-term disability in older cancer patients. Older cancer survivors more often have self-reported functional limitations compared to non-cancer controls[14-16]. Chemotherapy is increasingly offered to older adults[11,17] and often represents an acute stress, which can result in functional decompensation akin to that reported post-myocardial infarction[18]. Functional impairment as a consequence of initial treatments may impair quality of life, compromise independence, limit future therapeutic options, and increase mortality[8]. Our preliminary work among older adults with AML demonstrates dramatic objective declines in physical function shortly after receipt of chemotherapy (Section 11.C.7). Multiple factors likely contribute to post-chemotherapy-related functional decline, including increased acute and chronic side effects among older adults[19,20], and decreased physical activity during and after treatment[21]. Unfortunately, oncology clinical trials to date have not addressed preservation of function as an outcome of therapy.

Physical activity interventions may minimize chemotherapy-associated disability. There is substantial evidence to support the benefits of physical activity on physical function in younger adults with cancer[3,6,22,23]. Most trials have been conducted in long-term cancer survivors[24-31]. Recently, a few randomized trials have demonstrated improved physical function, muscle strength, and physical performance when supervised exercise occurred during chemotherapy treatment[32-37]. This approach focuses on prevention of functional decline when patients are at greatest risk. Two small studies specifically investigated the potential benefits of exercise in AML inpatients receiving intensive chemotherapy[38,39]. Both showed improvements in symptoms; patients in the randomized study also had improved physical performance[39]. Physical activity interventions delivered during active treatment may improve short-term physical function, minimize long-term disability, and increase quality of life.

Few physical activity intervention studies have been done in older cancer patients. Observational data support a positive association between exercise and higher self-reported physical functioning among older cancer survivors[40]. Two randomized home-based exercise interventions have demonstrated improved self-reported physical function in older cancer survivors[4,41]. **No published studies have focused on enrolling high-risk older adults actively receiving chemotherapy, as in our pilot study[2]** (Section 11.C.1). Many potential challenges exist in developing effective physical activity interventions for older cancer patients, such as recruitment and retention[41]. Increased comorbidity, lower physical activity levels, and worse functional status compared to younger patients at baseline also pose a challenge. For example, in our pilot observational data, most older adults with AML evaluated for induction chemotherapy met criteria for impairment in one or more geriatric domains (physical function, cognitive function, comorbidity, psychosocial function)[42]. Yet research to prevent physical function decline in non-cancer affected older adults suggests that these challenges can be overcome[43,44]. In particular, tailoring interventions to the participants' baseline status can enhance efficacy and is essential when targeting the most vulnerable patients[45]. Applying principles from geriatrics research to the design of physical activity interventions for older cancer patients may identify strategies to improve their functional outcomes.

AML is a model disease in which to develop interventions to minimize chemotherapy-associated physical disability. We propose studying older adults with AML because: 1) the intense treatment renders patients at high risk for the outcome (decline in physical function); 2) the outcome can be measured within weeks; 3) treatment is relatively uniform; 4) frequent measurements are easy to obtain due to inpatient status; and 5) decline in physical function can ultimately be correlated with morbidity and survival in this population. AML is largely a disease of older adults (median age at diagnosis 67 years)[9,19]. The disease presents acutely and aggressively and requires intense chemotherapy for cure[46,47]. Initial (induction) chemotherapy is given in the hospital; inpatients stay a mean of 20+ days due to expected complications[48]. Consolidation chemotherapy is also required to achieve cure[47]. Selected older adults can benefit from curative chemotherapy treatment, but are at higher risk for morbidity and mortality than younger patients[19,49]. Decline in physical function after induction chemotherapy[50] may preclude consolidation treatment for older adults. Successful interventions in this population can be translated to other vulnerable populations in oncology and geriatrics.

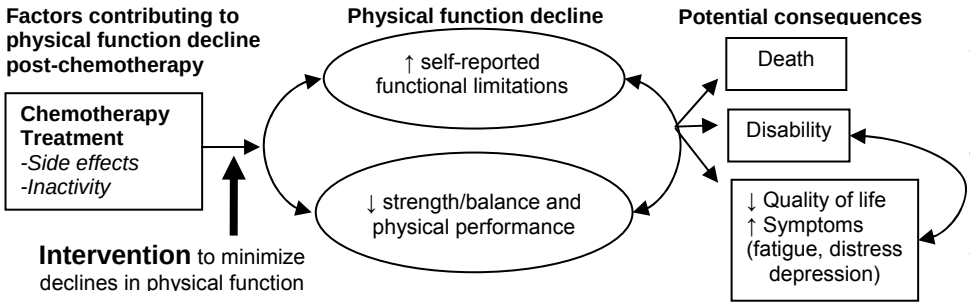
11. B. Innovation

This proposal has several innovations. 1) The target population, older adults receiving intensive chemotherapy, includes those at highest risk for subsequent physical disability. 2) A tiered symptom-adapted physical activity protocol is novel and adapts the intervention to the fluctuating status of frail older adults actively receiving treatment, which has broad implications for clinical translation. 3) We propose multiple validated measures of physical function developed specifically for older adults. The MAT-sf (Section 11.C.7), in particular, is an innovative practical new technology which may be uniquely suited to improve assessment of self-reported physical function in frail older adults from diverse backgrounds. 4) Developing an inpatient intervention addresses the huge and unattended problem of inpatient mobility issues[51-53] and provides unique access to the study population for frequent repeated measurements of function, interviews, and lifestyle-related counseling. Use of the clinical environment increases the likelihood that the intervention could be translated into usual care. 5) Lifestyle-related counseling (LC) is an additional mechanism to increase efficacy. Dr Rejeski has been a leader in developing this modification to physical activity programming for older adults[54] .

11. C. Approach

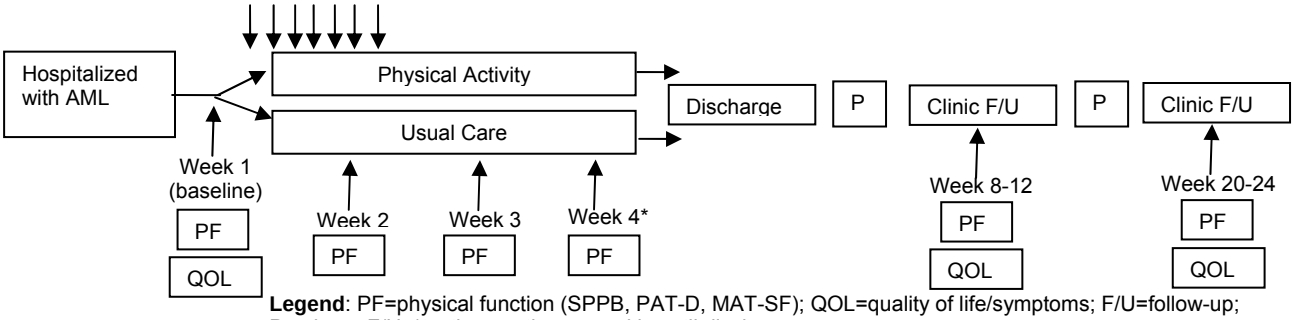
11. C. 1. Overview of Study Design: Our study posits that a physical activity intervention should minimize declines in physical function associated with chemotherapy in older adults with AML, leading to decreased disability and improved quality of life (**Figure 1**). Thus, following the schema outlined in **Figure 2**, we will enroll 70 adults 7 60 years of age undergoing induction chemotherapy for AML. Subjects will be randomized to either a physical activity or a control group. The intervention will be delivered for the duration of hospitalization and will consist of a symptom-adapted physical activity program with LC. LC will continue post-discharge with phone follow-up.

Figure 1. Conceptual model



Physical function will be measured weekly during the hospitalized intervention period. In-person clinic follow-ups will occur during weeks 8-12 and 20-24 from study enrollment with phone-based follow-up post-discharge. The **primary efficacy outcome** will be change in the SPPB. **Secondary outcomes** will include change in self-reported physical function, health-related quality of life, and symptoms (depression, distress, fatigue).

Figure 2: Study schema for exercise intervention study



Legend: PF=physical function (SPPB, PAT-D, MAT-SF); QOL=quality of life/symptoms; F/U=follow-up; P= phone F/U; *testing continues weekly until discharge

Our design builds on preliminary data including (1) a secondary data analysis confirming the association between physical performance and disability and death in older cancer patients[1]; (2) a small, non-randomized intervention (N=24) showing feasibility and safety of promoting physical activity among hospitalized older AML patients[2]; and (3) an ongoing observational study (current N=76) where 89% of eligible older AML inpatients have undergone pre- and post-chemotherapy functional assessment (including SPPB). In the latter study, preliminary analyses show significant declines in objective and self-reported physical function (Figures 3 and 4, Section 11.C.7.). Our study design and timeline fit the objectives of the career development plan (Section 3.0).

11. C. 2. Study Sample and Eligibility

Potential participants will be older adults hospitalized for chemotherapy treatment of AML at Wake Forest University Baptist Medical Center (WFUBMC). Eligibility criteria will be: (1) 760 years of age[19,55-57]; (2) Diagnosis of AML with pathologic confirmation by WHO criteria[58]; (3) Planned induction chemotherapy; (4) Absence of active medical problems that preclude participation in exercise (including, but not limited to,

bleeding, acute thrombosis, ischemia, hemodynamic instability, uncontrolled pain); (5) Ambulatory or able to walk with a cane; (6) Limited cognitive deficits (<3 incorrect responses on the Pfeiffer Mental Status Scale); and (7) Adequate English to understand the consent form and complete questionnaires. Approximately 40 adults 760 years old are admitted for treatment of AML at WFUBMC yearly. We aim to recruit 75% of eligible patients based on our previous experience with the current observational study (89%). We anticipate enrolling 70 subjects over 3 years. Given that recruitment to a randomized intervention may be lower than for an observational study, we project achieving our target sample even if recruitment falls to 60%.

11. C. 3. Recruitment and Randomization

Following successful recruitment strategies in place for our ongoing observational study, potential study participants will be identified by the Leukemia Team Nurse Coordinators and the Study Nurse (SN). The SN will confirm eligibility, approach patients for participation, and administer informed consent within 4 days of hospital admission. The responsible attending physician will also be notified before recruitment to confirm medical eligibility. After informed consent, subjects will undergo a baseline assessment performed by the SN and then be randomized to the physical activity protocol or usual care in a 1:1 ratio.

11. C. 4. Intervention Overview

The physical activity program will be a multi-modal, low intensity, frequently administered intervention based on our prior experience in this population and successful programs in older, frail populations[2,59]. Our observational data show declines in strength, balance, and gait speed (Figure 3) post-chemotherapy, supporting use of a multi-modality program. Participants in our prior intervention study had difficulty adhering to a fixed, infrequently offered (3X per week) intervention due to changes in medical condition and symptoms-highlighting key differences between our target population and those typically enrolled in outpatient interventions after completion of cancer treatments. Thus, we have developed a novel 3-tier symptom-adapted protocol (Section 11.C.4.a). The physical activity sessions will be administered by a physical therapist. This 1) increases generalizability by maximizing opportunities to integrate this type of intervention into practice, and 2) utilizes trained personnel experienced in performing a physical activity protocol at WFUBMC in the ICU[60]. LC will complement the physical activity program to enhance adherence and long-term behavioral change. Participants will receive phone follow-up after discharge to provide continued education/encouragement and assess barriers to continued physical activity (CDP,4b2).

1 1. C. 4.a. Outline of Intervention Components:

Physical Activity Program

Orientation Session: This initial session will introduce the exercise program and protocol, review the fundamental principles, and demonstrate each activity. It is modeled after the one-on-one visit in the LIFE study designed by Dr. Rejeski[59]. Participants will receive educational materials (CDP, Section 4b2) to facilitate orientation and adherence. Key members of the participant's support system will attend this session.

Physical Activity: Sessions will be offered **5 days per week** (adherence is defined as participation in an average of 3 or more offered weekly sessions). We will **tailor each session** to the patient's daily condition to maximize participation and benefit (see tiers below). The interventionist will first check with the patient's nurse to identify medical contraindications to physical activity[2]. If contraindicated or the patient declines participation, the interventionist will check daily to determine appropriateness to resume. This method was utilized in our prior study and helps ensure safety. If there are no contraindications, the subject will be offered a standard session, intermediate or low-intensity session; this will be a collaborative decision based on the interventionists. assessment and the patient's preferences[61]. Intensity of training will be regulated using the Rating of Perceived Exertion (RPE) Scale[62 43] and heart rate as done in our prior pilot study[2].

Standard Session (Ward-based): Each standard session will include cardiovascular, resistance, flexibility and balance training. The session will begin with a 2-3 minute warm-up phase (walking in place, mild stretching). This will be followed by 10 minutes of walking on the medical ward[2], at a rating of perceived exertion (RPE) from 12-14. Duration and intensity of the walking segments will be individualized, emphasizing mild intensity levels and a gradual progression in duration. Participants will then do approximately 10 minutes of strength and flexibility exercises. The strength exercises will utilize resistance bands to ensure maximal safety and control and were well received in the prior pilot study[2]. The protocol will include the following 10 potential exercises: chest press, back row, biceps curl, triceps press, shoulder raise, torso twist, leg raise, leg curl, and calf point. Five will be chosen for each session to target large muscle groups of the upper and lower body[2]. Range of motion (ROM) exercises will be performed following the strength phase to increase flexibility[63]. Participants will then do 10 minutes of graduated balance training, modeled after that used in the LIFE study[59]. The session will conclude with a 3-5 minute cool-down/stretching phase. Each session will range from 45-50 minutes. All participants will be given two resistance bands and guidelines for continuing activities upon discharge.

Intermediate Session (Room-based): The intermediate session can be done entirely in the patient's room. In our pilot study, 45.3% of exercise sessions were in-room only (despite offering walking as the cardiovascular component)[2]. Therefore, we will offer use of an upper-body ergometer for the cardiovascular component, which has been successfully utilized in prior studies among younger hospitalized patients receiving intense chemotherapy and in the ICU[64,65]. Participants will be instructed to perform 10-15 minutes of biking in the seated position using the upper-body ergometer, at an RPE of 12-14. Subjects will be offered resistance, flexibility, and balance training as reported above. This session will range from 35-40 minutes.
Low-intensity session (Bed-based): The low-intensity session can be done by patients entirely in their beds. This session utilizes components of successful interventions performed with patients in an ICU, including work at WFUBMC[60,64]. Even short-interval, low-impact physical activity can improve outcomes for hospitalized frail adults[64]. Subjects who are unable/unwilling to perform activities out of bed will be offered the following: 1) 10 minutes of graded cardiovascular activity on the upper body ergometer (RPE 12-14) in the supine position; 2) progressive resistance exercises using resistance bands. This session will be 20-25 minutes.
The Lifestyle-related Counselling (LC) Component:
Participants randomized to physical activity will also receive a 20-30 minute LC session weekly during hospitalization with post-discharge phone follow-up, performed by the SN, designed to 1) discuss costs and benefits experienced in the past week; 2) review progress; 3) highlight consequences of deconditioning and benefits of physical activity during treatment and post-discharge; 4) establish self-regulatory skills for effective behavior change; 5) discuss and trouble shoot barriers to adherence[59]; and 6) establish specific goals for the coming week. The program will focus on the patient, with caregivers (friends/family) encouraged to participate. A written protocol with educational materials will be developed in the CDP (Section 4.b.2). Post-discharge phone follow-ups will be done every 2 weeks for 2 months, and then monthly until week 24.
11. C. 5. Control Group
Participants in the control group will receive usual care, which may include physical therapy (PT) at the discretion of the attending physician. At our hospital, PT is typically consulted just before discharge. The SN will interact with control participants weekly to perform physical function assessments. Since a usual care-only control may pose a challenge to recruitment, we will monitor this (CDP, 4.b.2) and add a non-exercise based educational component if this is the primary barrier identified during Year 1 of enrollment.
11. C. 6. Study Procedures, Data Collection, Management and Follow-up
Data will be collected by the SN, including baseline (Week 1) with weekly physical function measures during hospitalization. Subjects will be tracked by the SN; clinic follow-up assessments will be done during routine clinic visits to minimize participant burden. This method has been successful in our observational study, with 93% retention to date. Vital status will be ascertained by the CCCWFU cancer registry. Validated and standardized forms will be used to ensure quality control. The SN (who performs assessments in our observational study) will be trained in administration and scoring of new survey measures and performance testing by Pepper Center personnel, and in delivering LC sessions, supervised by Dr Rejeski. A written protocol for administration and scoring of tests will be utilized. All participant data will be transferred into a web-based data entry system by a data manager from the CCCWFU, a service available to all cancer center trials.
11. C. 7. Outcome Assessment
Feasibility Outcomes (Aim 1)
To inform a future R01 grant proposal, feasibility is of primary interest in this pilot study. Measures will include: 1) recruitment (760%); 2) adherence (percentage of participants performing an average of 3 sessions per week); and 3) retention (85% completion rate of follow-up assessments for available participants). Additional qualitative data will be collected through the design of survey measures (CDP, 4.b.2) to evaluate barriers to recruitment, adherence from the standpoint of the participant and caregiver (family/friend) support. A participant feedback survey will also be developed to be administered post-intervention (prior to discharge) to assess perceived benefits of and satisfaction with the overall program and its components.
E fficacy Outcomes
Primary outcome (Aim 2): Change in the **SPPB** is the primary variable of interest to assess objective changes in physical function and will be used for sample size calculations for R01 development. This validated measure is comprised of a short walk, repeated chair stands, and balance test [66,67]. Each performance

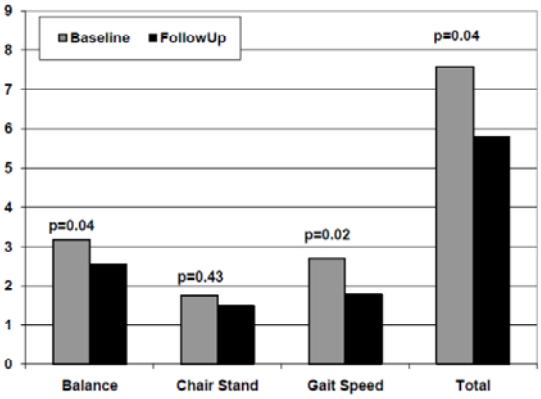


Figure 3: Change in SPPB from baseline (pre-chemotherapy) to clinic follow-up (post-chemotherapy) among older adults receiving induction chemotherapy for AML (N-35). These data illustrate clinically significant objective declines in total and component scores of the SPPB.

measure is scored ranging from 0-4 (0 = unable to complete; 4 =highest performance level), with total sum score range from 0-12 [66,67]. The SPPB is responsive to an exercise intervention[43] and our preliminary data show that SPPB total and component scores decline post chemotherapy (**Figure 3**).

Secondary outcomes (Aim 3):

Self-reported Physical Function:

The Pepper Assessment Tool for Disability (**PAT-D**) is a 19-item survey designed by Rejeski et al. to assess domains of physical function in older adults[54,68-70] which contains subscales on mobility, instrumental (IADLs), and basic activities of daily living (ADLs) [71]. Participants answer questions on a Likert scale ranging from 1 (usually did with no difficulty) to 5 (unable to do). A total summary score and subscale scores result, with higher scores indicating greater functional limitations. This survey is sensitive to change in the AML population (**Figure 4**). It is used in all Pepper Center-supported studies, allowing comparisons to other populations (CDP, 4b1).

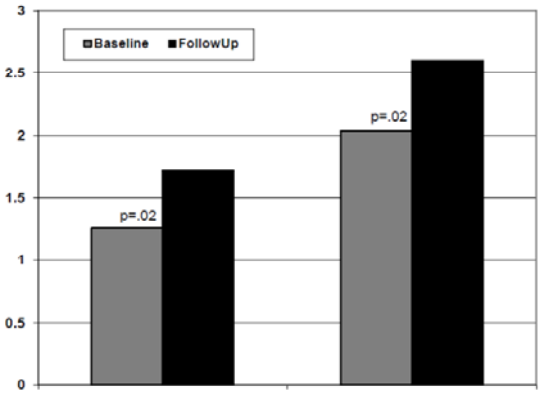


Figure 4: Change in self-reported physical function (subscales of the PAT-D survey) from baseline (pre-chemotherapy) to clinic follow-up (post-chemotherapy) among older adults receiving induction chemotherapy for AML. Higher scores post-chemotherapy indicate significant increases in IADL and mobility limitations post-treatment.

The Mobility Assessment Tool (short form) **MAT-sf** is an innovative 10-item computer-based assessment of mobility using animated video clips developed by Rejeski et al[72]. The use of animation: a) removes potential biases in interpretation and b) standardizes within-item variables. Items range in difficulty from walking slowly on level ground to climbing stairs while carrying bags. Respondents assess their ability to perform the displayed activity. The 5-minute test can be done on any laptop and has excellent test-retest reliability (r=0.93) and validity[72].

Health-related Quality of Life: We will use the Functional Assessment of Cancer Therapy-Leukemia **(FACT-LEU)** to evaluate health-related quality of life. This contains the well-validated Functional Assessment of Cancer Therapy (FACT-G) assessment and a leukemia-specific subscale[73]. The FACT-G is a 28-item questionnaire with 4 subscales: physical, social/family, emotional, and functional well-being[74]. The leukemia-specific subscale contains 17 items focused on symptoms (i.e. fevers, chills, bleeding). We found this measure sensitive to change over time (**Figure 5**)[2]. The FACT-LEU survey will be given at baseline, and during clinic follow-ups.

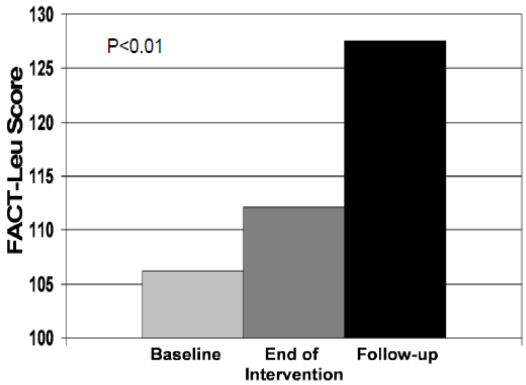


Figure 5. Change in FACT-Leu during non-randomized pilot study in older AML patients receiving chemotherapy (N=11). Higher scores post intervention reflect significant improvement in reported quality of life.

Symptoms: Depressive symptoms will be assessed using the Center for Epidemiologic Studies Depression Scale (**CES-D**), a 20-item scale with demonstrated excellent validity and reliability in the geriatric population[75]. Distress will be assessed using the **Distress thermometer**[76,77]. Both have been used in cancer populations including AML. Our previous work showed that these measures detect abnormalities in this population[42], are sensitive to change over time, and may be influenced by an exercise intervention[2]. Fatigue will be assessed using the validated 13-item **FACT-fatigue** Scale[78,79]. Fatigue is the most common complaint of patients[80-82] receiving cancer therapy and may be improved by physical activity interventions[38,83,84].

Exploratory Outcomes:

We plan to obtain repeated measures (weekly) of upper and lower extremity strength during hospitalization. Grip strength in both hands will be measured by using an adjustable, hydraulic grip strength dynamometer, as done in previous studies[85,86]. Our observational data suggest grip strength is sensitive to change over time (prechemotherapy 34.2 kg, post chemotherapy 30.7kg, p<0.001). Lower extremity strength will be evaluated using the Lafayette Manual Muscle Test System. This hand-held dynamometer tests quadriceps strength in older adults and correlates well (r=0.91, p<0.0001) with results from Biodex dynamometry[87]. Two trials will be done on the non-dominant leg, in a supine position, with the leg flexed at a 35°angle[87]. The primary limitation is

underestimating strength in subjects who are particularly strong[87]. Given that many participants will be acutely ill, and previous SPPB testing has shown low mean scores, this should not be a significant issue.

Additional Variables of Interest:

At initial admission, we will collect from chart review: 1) demographics; 2) clinical parameters (hemoglobin, creatinine, comorbidity burden-estimated by the Hematopoietic Cell Transplantation Comorbidity Index (HCTCI)[42,88,89], body mass index; and 3) AML-specific variables (white blood cell count, LDH, and cytogenetic risk group)[90]. We will also track timing and duration of chemotherapy, timing and frequency of PT as part of usual care, length of hospitalization, treatment-related mortality[19] and overall survival.

11. C. 8. Power and Statistical Analysis.

Power. The sample size for the RCT (N=70) is based on estimating retention rates and effect sizes to inform a larger efficacy trial. Assuming about 120 eligible participants, we feel confident that the recruitment rate is >60% when the observed recruitment rate is as small as 68% (the lower limit of a one-sided 95% CI is 61%). We anticipate that about 15% of 70 participants will die before the first follow-up assessment. Of the remaining participants, we would be confident that the retention rate is >77% when the observed retention rate is 85%, and that the adherence rate is >65% when the observed adherence rate is 75%. With this sample size (n=30 per group), if we observe no difference in change in SPPB from baseline to the first follow-up between the intervention and usual care groups, we would like to be able to rule out that the effect size is not greater than 0.5. The upper limit on the one-sided 95% CI for an effect size of 0 is 0.43 with this sample size.

Statistical Analysis. To assess feasibility for **Aim 1**, we will track participation rates and barriers to recruitment and retention. We will record number of exercise sessions completed, dropout rates, completion rates of the physical function measures, completion rates of questionnaires. For **Aims 2 and 3**, we will characterize the magnitude and trajectory of changes in objective physical function (Aim 2) and self-reported physical function and quality of life (Aim 3), using mixed model ANOVAs with an appropriate error structure to account for the correlated nature of the data. Specific contrasts will be constructed to examine: the rate of decline 1 week after chemotherapy, the time period in the trajectory which exhibits the steepest decline in function, and to test whether physical function is regained in the follow-up time period, remains flat, or continues to decline; we will compare differences in these trajectories between groups to obtain estimates of effect size. Because we lack preliminary data on this trajectory, it is difficult to anticipate how many contrasts will need to be constructed; however, we will control for experiment-wise error rate.

11. C. 9. Strengths and Limitations

The proposed research study has some limitations. There is a potential lack of generalizability due to performing the study at a single institution. We believe a single-site study is acceptable given the scant data in this area. A single-site study allows us greater control to assure its internal validity. Results will require validation, such as the proposed multi-site intervention study to be designed in the CDP. In addition, studying AML patients also limits generalizability. Physical function decline may be more pronounced in AML and physical activity interventions will be more challenging. However, AML is a useful model to investigate the principles of functional decline and tailored interventions highlighted in this RP (Section 11.A.). We anticipate that lessons from this population will apply to other cancer types in the in- and out-patient settings.

The proposal also has several strengths. The RP and CDP build logically upon a strong foundation of prior work. Chemotherapy-associated physical disability has significant public health implications and has been neglected, particularly among older adults. We propose testing an adaptable physical activity intervention based on careful observations of functional decline in a specific patient population. This type of informed intervention may not only improve treatment outcomes of older adults with AML, but also be a model for developing similarly tailored interventions for older adults with other types of cancer. By successfully translating principles of geriatrics and exercise science into an extremely vulnerable cancer population, this study provides a needed foundation for research on disability prevention in oncology.

11. C. 10 Research Plan Timeline

Research Aims	Year 1				Year 2				Year 3				Year 4				Year 5			
Protocol development																				
IRB submission/ Training																				
Recruitment to exercise intervention																				
Follow-up for exercise intervention																				
Data analysis/ manuscript writing																				
Prepare/apply for RO1																				