Specific Aims: The goal of this *Mentored Patient-Oriented Career Development Award (K23)* is to acquire the skills and experience necessary to become an independent investigator in the assessment and treatment of diagnostically complex older adults by focusing on elders with depressive illness and the syndrome of frailty. Late life depression[1-8] and frailty[9-12] are each associated with worsening disability, increased falls, hospitalizations, and death, resulting in decrements in quality of life for patients and families, and dramatic increases in health care costs. *No one to date however has explicitly studied the depressed, frail phenotype*.[13,14] This is surprising as frailty, a syndrome of decreased resiliency[9] resulting from declines across multiple physiologic systems and characterized by weakness, slowness, low physical activity, exhaustion, and unintentional weight loss, appears to be *phenomenologically* and *physiologically* associated with depression.[15] Frailty shares characteristics common with late life depression (*psychomotor slowing, weight loss, decreased activities, low energy*) and the rate of depressive symptoms in elders increases proportional to the number of frailty characteristics present.[9] Additionally, depression and frailty are both associated with elevated levels of interleukin 6 (IL-6) and C-reactive protein (CRP),[16-23] as well as malnutrition.[24-28] Despite these associations, frailty has remained a focus of study for geriatric medicine and outside the purview of psychiatry.[13,29] Thus the interrelationships between depression and frailty, and the implications for the psychiatric treatment of these diagnostically complex geriatric patients have gone unstudied.[13]

The presence of factors such as executive dysfunction[30-34] and white matter hyperintensities[35-38] attenuates response to antidepressant medication in late life depression. The presence of frailty, a syndrome that operationalizes physiological declines, may also impact depression treatment. The issue is complicated however by the diagnostic complexities of the depression-frailty relationship itself. In two late life depressed samples (n=164; n=24), one from a placebo-controlled antidepressant trial of elders with moderate-to-severe medical comorbidity, the other from an open-label antidepressant trial, 99% and 96% respectively met criteria for prefrailty (n=63, n=17) or frailty (n=100, n=7). Thus the diagnosis of major depression appears redundant with frailty classification, seemingly rendering the construct of frailty in depression meaningless. This is not however the case: secondary data from the Nordic Research on Ageing study[39,40] show that risk of death in elders with deficits in grip strength and/or gait speed was 1.5 times greater compared with those without these deficits; this risk increased to 2.11 when depression was present. Pilot data also show that only 40% of depressed elders with deficits in grip strength and/or gait speed responded to antidepressant medication compared to 100% of depressed elders without these deficits. Based on these data, I constructed a *model of the depressed, frail phenotype*. I hypothesize that depressed patients with deficits in gait speed, grip strength, and/or weight loss will have attenuated response to antidepressant treatment and less long-term improvement in disability compared to depressed patients with decreased activity and/or energy levels (i.e. only those characteristics of frailty that overlap with symptoms of depression). I believe that patients with these physical frailty deficits will have elevated IL-6, CRP, and lower serum albumin levels at baseline.

To test this model, I propose a 12-month deconstruction of the frail, depressed phenotype. I will conduct an open-label antidepressant trial of escitalopram or duloxetine (Acute Phase) followed by a 10-month Follow-up Phase in late life ($\geq$65 years), depressed (DSM-IV diagnosis of Major Depression or dysthymia; Hamilton Rating Scale–Depression, HRSD[41]$\geq$16) patients (N=60) with $\geq$ 1 frailty characteristic. I have constructed a multidisciplinary training plan focused on 1) the assessment and understanding of the biological, neuropsychological, and physical characteristics common to frailty and depression, and 2) the design and conduct of interventions. My research plan is exemplary of the NIMH's Research Domain Criteria (RDoC) by classifying patients along both Cognitive and Physical systems and using multiple units of analysis (self-report, physiological, and behavioral data) to assess these systems. With this experience and skill set, I can bridge the gap between geriatric medicine and psychiatry and undertake a research career using comprehensive, multidisciplinary assessment to personalize interventions for diagnostically complex geriatric patients.

Specific Aim 1: **Acute Phase**: Evaluate the effect of antidepressant medication in depressed, frail patients.

Hypothesis 1: Patients with no deficits in gait speed, grip strength and/or weight loss will show greater reduction in depressive symptoms (HRSD) than will patients with these deficits. *Hypothesis 2*: Patients with no deficits in gait speed, grip strength and/or weight loss will show a greater reduction in frailty characteristics compared to patients with these deficits.

Specific Aim 2: **Follow-up Phase**: Evaluate long-term effects of antidepressants in depressed, frail patients.

Hypothesis 3: Patients with no deficits in gait speed, grip strength and/or weight loss will show greater improvements in *disability* (Short Physical Performance Battery,[42] World Health Organization Disability Assessment Scale 2.0,[43] Everyday Measure of Cognition,[44] and actigraphy[45]), and *markers of inflammation and malnutrition* (lower CRP, IL-6; higher serum albumin) compared to patients with these deficits**.**

2. Candidate Background

I have spent the last 12 years acquiring the skills necessary to undertake a career focused on alleviating the disability and improving the quality of life for older patients with neuropsychiatric disorders. My introduction to geriatrics and clinical research took place junior year at the College of the Holy Cross. My Research Methods professor, Andrew Futterman, PhD, noted my interest in clinical research and we began a collaborative investigation of the bereavement process in older adults, comparing data to existing theory through the use of factor analytic and structural equation methods.[46] This collaboration led me to seek out more research experiences senior year as a research assistant at University of Massachusetts Medical Center assessing cognition in older nursing home residents. The experience of observing these older adults with comorbid medical illness negotiating their own environments remains evident in my recent work on disability and function in late life, and is reflected in this protocol through the study of older adults manifesting symptoms of the depressed, frailty phenotype, and in the evaluation of change across domains of function and mobility in this population. After graduating I worked as a clinical research coordinator in the Gerontology Research Unit at Massachusetts General Hospital directed by Marilyn Albert, Ph.D. I was trained in neuropsychological assessment, anxiety and depression screening, and the Clinical Dementia Rating (CDR) scale. I coordinated an antidepressant clinical trial comparing mirtazapine to paroxetine and coauthored two papers, a review on the effect of cholinesterase inhibitors on behavior in demented elders[47] and an open-label trial of D-cycloserine and donepezil for treating Alzheimer's disease (AD).[48]

To confirm my desire to return to graduate school, I applied my skills and interests in the private sector at a consulting firm for two years conducting health economics research. After earning enough money for graduate school and affirming the pursuit of my clinical interests, I entered the Clinical Psychology program at Washington University in St. Louis. I am still in awe of the research and clinical training in psychology and geriatrics I received under the tutelage of Martha Storandt, PhD. This training resulted in a project that I planned and executed investigating the underlying factor structure of the Geriatric Depression Scale.[49] This project showed in a sample of older depressed patients and an independent sample of cognitively impaired elders that although both reported elevated depression scores, the pattern of item endorsement differed by group with cognitively impaired older adults endorsing degradations in life satisfaction rather than depressive affect. I continued to pursue research opportunities in clinical gerontology, collaborating with Brian Carpenter, Ph.D. and John Morris, M.D. on a project exploring the psychological effects of receiving a diagnosis of dementia.[50] As part of my dissertation I conducted an extensive assessment of domains of quality of life, positive and negative affect, personality, and depression and anxiety in 443 individuals ages 30 to 98, finding that, despite the myth that quality of life decreases with age, Psychological, Social, and Environmental quality of life either remained the same or increased with age; only Physical quality of life decreased with age.[51] Following graduate school, I completed my clinical internship at Montefiore Medical Center in the Bronx, NY where I continued to specialize in geriatrics under the guidance of Gary Kennedy, MD, an investigator of disability in late life depression and the former President of the American Association for Geriatric Psychiatry. Although my clinical opportunities in St. Louis were primarily limited to Caucasians, at Montefiore I worked with Dominican, Puerto Rican and African American populations. These experiences better prepared me for my current position working with the ethnically diverse populations of the Washington Heights area of Manhattan.

Spurred by lingering questions from past clinical and research experiences, I pursued a career in clinical research, applying to the T32 NIMH Geriatric Psychiatry fellowship at Columbia University. My interest in disability in older adults struck a cord with my primary mentor, Dr. Steven Roose. Dr. Roose's experience as principal investigator of a multicenter, double-blind, randomized 8 week trial comparing citalopram to placebo in depressed patients 75 and older[52] with comorbid medical illness led him to pay specific attention to the disability that accompanied these patients.[52] The synergy of interests with my mentor and colleagues led to a productive collaboration during my fellowship. I led two projects in my first year, one evaluating the characteristics and correlates of functional impairment in individuals with amnestic MCI (aMCI) which was published in the *Archives of General Psychiatry*,[53] and the other investigating the moderating effect of psychiatric symptomatology on the relationship between age and quality of life.[51] I was awarded a $25,000 2010 Jr. Investigator Award from the National Alzheimer's Coordinating Center (NACC) to conduct secondary data analyses examining functional impairments in MCI, reporting in the *American Journal of Geriatric Psychiatry* the finding that processing speed decrements play a mediating role between depression and executive dysfunction and functional impairment in older adults with MCI.[54] I attended Summer Research Institutes (SRI) for future independent clinical researchers in aging (NIA, 2010) and geriatric psychiatry (NIMH, 2010), and finalized collaborative manuscripts studying bereavement,[46] social anxiety,[55] symptom onset predicting conversion to dementia,[56] and the clinical utility of an algorithm for the transition from MCI to

dementia.[57] Currently I have four manuscripts under review; two first author studies that are focused on 1) frailty and depression and mortality in late life and 2) the need for comprehensive assessment in cognitively impaired older depressed patients, and two collaborative studies on 1) the effect of visit frequency on treatment response in antidepressant clinical trials and 2) social anxiety in older adults.

These scientific accomplishments were completed while attending courses in statistics, research design, grant writing, and responsible conduct of research as well as obtaining my license in Clinical Psychology in the State of NY (#019153-1). My interest in function and psychiatric symptomatology led to the formation of a collaborative relationship with Dean Linda Fried (Scientific Advisor), who operationalized the prevailing characteristics of the construct of frailty. The obvious synergy between Dr. Fried's specialty and my interest in disability has helped give rise to the research track outlined in this proposal. I believe that the depressed, frail phenotype is the most promising avenue available for making inroads to understanding how to improve mental health treatment outcomes for geriatric patients with diagnostically complex medical and psychiatric comorbidity. Through my assessment of disability, mobility, and frailty in older adults with depression in the Adult and Late Life Depression Clinic (ALLDC; IRB #6213; IRB #6470), and at Kendal on Hudson (IRB #6608), as well as the secondary data analysis of the Nordic Research on Ageing study, I present pilot data in this proposal that support my hypothesis that there may in fact be two clusters of depressed, frail older adults, and that these symptom profiles may predict divergent clinical trajectories and responses to depression treatment. Through my pilot data and my conversations with my mentoring team, it became apparent that because frailty and depression are studied separately, the nature of the phenotype remains unclear, and questions remain about how best to treat what could be the most vulnerable geriatric population.[58-61] With Dr. Roose, Dr. Fried, and a team of physical therapists and nutritionists, I submitted an R21 application to test the feasibility of treating a depressed, frail population with a sequential intervention that targets depression initially with antidepressant medication, followed by an intensive exercise and nutritional intervention designed to treat the characteristics of frailty. The reviewers felt that, although the project "could have a significant impact on the field" with "high public health significance", I needed to obtain more data to support my hypotheses and garner more training before I led such an intervention project. The critiques provided evidence for the need for this current K23 proposal. With this K23, I am attempting to deconstruct the phenotype using antidepressant medication, and develop skills for multidisciplinary assessment and intervention implementation. Together, the research and training from this K23 will enable improved treatment planning through the refinement of our understanding of this complex phenotype and result in future intervention research. This trial represents a development opportunity and a critical building block for a career investigating the phenomenology and treatment of medically complex geriatric patients with neuropsychiatric disorders. My research experiences at Columbia University, focused on disability in late life neuropsychiatric disorders, have led to the establishment of a multidisciplinary team of experts who will aid in my development in the comprehensive (phenomenological, biological, and neuropsychological) assessment and targeted treatment of diagnostically complex geriatric patients.

3. Goals and Objectives

As stated, I want to contribute to the improvement of the quality of life of older adults with neuropsychiatric disorders. M. Powell Lawton[62] hypothesized that maladaptive behaviors and emotions result from the interplay between one's ability and environmental demand. As characteristics of frailty and symptoms of depression increase, the capacity to manipulate and negotiate the environment worsens. This leads to decrements in daily activities that markedly affect quality of life. I will continue the pursuit of alleviating disability through a research career focused on refining the depressed, frailty phenotype, and developing targeted interventions to improve prognosis. With the submission of this proposal, I embark on two major research and training objectives:

Objective 1: *Undertake a research career parsing the complex psychiatric-medical phenotypes typical in geriatric patients and using the resulting information to develop personalized, targeted interventions; this initial project will investigate the effect of the depressed, frail phenotype on antidepressant pharmacotherapy*.

The research and training plans outline the first steps in a career spent refining the assessment of diagnostically complex, depressed older adults, investigating critical dimensions of heterogeneity within this highly comorbid group, and how this heterogeneity impacts prognosis and treatment outcomes. This initial project will serve as a foundation for understanding the phenomenological and biological relationships between depression and frailty, and the development and implementation of personalized treatments.

Objective 2: *Forge relationships with colleagues across disciplines to foster a deeper understanding of the physical, neuropsychological, and biological complexity of geriatric patients, which will allow me to serve as a bridge between geriatric medicine and psychiatry and form a network for future cross-disciplinary projects*.

I have established a multidisciplinary team from whom I will gain knowledge in the biological, neuropsychological, and physical complexity of the geriatric patient, as well as learn the intricacies of providing interventions in this clinical population. Through coursework, activities, and consultations with this team, I will improve my understanding of the complex relationship among markers of inflammation, malnutrition and the behavioral manifestations of disability, frailty, and depression. With increased phenomenological, neuropsychological, and interventions expertise, I can combine the knowledge gained from both geriatric medicine and psychiatry for the study of personalized treatments of depressed, frail elders. What follows is a training plan focused on the attainment of skills necessary for my development as an independent researcher.

4. Career Development/Training Activities During Award Period

This *K23* training plan (Table 1) outlines how I will attain the skills to become an expert in the assessment and treatment of diagnostically complex geriatric patients with neuropsychiatric disorders. The training team:

Primary Mentor: **Steven P. Roose, MD**, is a Professor of Clinical Psychiatry at Columbia University College of Physicians and Surgeons and Director of the ALLDC. He is the PI for the T32 Research Fellowship in Affective and Anxiety Disorders and the T32 Research Fellowship in Late Life Neuropsychiatric Disorders. He is an experienced interventionist and recognized expert on the clinical, demographic, and treatment factors affecting response to antidepressants.[52,63] Dr. Roose's track record helping young investigators develop research careers makes him an ideal choice for Primary Mentor. While Dr. Roose does not currently have independent funding beyond being PI on two T32 training grants, he is an active mentor in Geriatric Psychiatry. We have an active research group studying vascular depression (Sneed – Dr. Roose primary mentor on his K23), depression and cognitive impairment (Devanand), augmentation treatment of nonresponding elders (Rutherford, Sneed) and the placebo effect (Rutherford – Dr. Roose primary mentor on K23).

Co-Mentor: **Mathew Maurer, MD,** is an Associate Professor of Medicine and director of the Cardiovascular Research Laboratory for the Elderly (CRLE). He is a cardiologist, researcher, and experienced mentor with a K24 and research interests in the relationship between cardiovascular health and anergia in older patients.[45,64]

Scientific Advisor: **Linda Fried, MD**, Dean of the Columbia University Mailman School of Public Health, is a geriatrician, epidemiologist and pioneer of the operationalization of the frailty syndrome concept.[9-11,19,65-67]

Scientific Advisor: **Meryl Butters, PhD**, Associate Professor of Psychiatry at the University of Pittsburgh and expert in the neuropsychological impairment that accompanies late life depression.

Scientific Advisor: **J. Craig Nelson, MD,** Leon J. Epstein, MD Endowed Chair in Geriatric Psychiatry at the University of California San Francisco and expert in the pharmacological treatment of late life depression.

Scientific Advisor: **Sue Marcus, PhD,** is an Associate Professor of Biostatistics (in Psychiatry) and Research Scientist VIII at Columbia University and expert in the design and analysis of mental health interventions and experienced biostatistician on psychiatric intervention studies.

Scientific Advisor: **Paul Appelbaum, MD**, the Elizabeth K. Dollard Professor of Psychiatry, Medicine and Law, and Director, Division of Law, Ethics and Psychiatry at Columbia University, has been elected to the Institute of Medicine of the National Academy of Sciences and runs the Ethics Workshop for the Irving Institute.

1. THE COMPLEX GERIATRIC PATIENT (Years 1-5): To bridge the gap between geriatric medicine and psychiatry, I have designed a track focused on knowledge acquisition in a) the biological mechanisms associated with aging, the syndrome of frailty, and the interaction between disability, physical weakness, mobility disturbance, and markers of chronic inflammation, b) the assessment of frailty characteristics, c) inflammation in depression, and d) how cognitive impairment impacts the association between frailty and depression. This training track focuses on assessing and understanding the trajectories of the depressed, frail patient through multidisciplinary assessment methods including the use of actigraphy, neuropsychological measures, and biological markers of inflammation as surrogate end points for treatment outcomes.

Activities: *Knowledge acquisition via readings* on the biology of aging, inflammation in the aging body, the correlation between elevated CRP, IL-6 and prognosis in geriatrics (Maurer, Fried), neuropsychology in late life neuropsychiatric disorders using select chapters from Lezak[68] and Kaplan[69] (Butters), and on inflammation in late life depression (Roose); *Skills acquisition via manuscript preparation* using 1) data from Dr. Maurer on physical activity in older patients with heart failure, 2) data from the Nordic Research on Ageing (NORA) study, 3) data from NACC, and 4) data from this project. *Skills acquisition via frailty assessment experience* in the ALLDC, the CRLE, and at Kendal on Hudson (IRB # 6608).

Advisory: **Mathew Maurer, MD** and I will meet twice per month from Years 1-5. These meetings will follow three training components: 1) *Selected Readings*: Dr. Maurer will provide expert guidance in a) the relationship between anergia, the pathophysiology of the syndrome of frailty and how they relate to my hypothesized model of the depressed, frail phenotype, and b) the assessment of mobility and activity in geriatric patients (including techniques such as actigraphy, which will be used in this project). 2) *Practicum in cardiology*: I will conduct under the supervision of Dr. Maurer the assessment of frailty characteristics and depressive illness in nondepressed older patients with cardiologic dysfunction in the CRLE to evaluate the similarities and differences between depression and the syndrome of frailty. I will attend their monthly laboratory staff meetings to gain knowledge in the approach to treatment planning and patient care in geriatric medicine. I will gain knowledge and experience in the implementation and use of actigraphy. 3) *Manuscript preparation*: Dr. Maurer and I will collaborate on manuscripts using data from his laboratory on activity levels in heart failure patients, and utilize data from the Cardiovascular Health Study (as he is a member of the Clinical Cardiovascular writing committee) to investigate the relationship between specific characteristics of frailty and outcome in patients

with elevated depressive symptomatology. **Linda Fried, MD** and I will meet quarterly from Years 1-5 on the concept of frailty and disability in geriatric patients. The consultation will focus on the theoretical framework for Dr. Fried's research on frailty, the pathology of sarcopenia, understanding and interpreting inflammatory markers such as CRP and IL-6 in frail elders and how these markers are associated with individual characteristics of the frailty syndrome and disability. In Years 3-5, the consultation will focus on the design and implementation of nonpharmacologic interventions that target the physical manifestations of the frailty syndrome, in an attempt to capitalize on Dean Fried's experience designing Experience Corps as an intervention to prevent frailty and disability. I will also participate in the monthly meetings of the Women's Health and Aging Study to develop multidisciplinary collaborations that will build on my development as an expert in the phenomenology of the depressed, frailty phenotype and the assessment of the frailty syndrome. **Meryl Butters, PhD** and I will speak via teleconference quarterly and meet annually at the annual American Association for Geriatric Psychiatry (AAGP) conference. The purpose of this portion of training is to go beyond my training in assessment to develop a broader knowledge base in the association between brain pathology and cognitive function in older adults in the frail, depressed phenotype. Dr. Butters and I will assess the data from this protocol quarterly, comparing the evolving trends with data Dr. Butters has collected from a late life depressed sample in Pittsburgh. In combination with readings from Lezak and Kaplan on the neuropsychology of aging, these training experiences will help me build a model of brain dysfunction based on the neuropsychological profiles of patients with differing presentations of the frailty syndrome. This model will link neuropsychological function with possible neuropathology in these frail, depressed patients and inform future studies (including the use of neuroimaging techniques) on these complex patients. **Steven P. Roose, MD**, while lending his expertise to my development as an interventionist (see below), will guide me in our formal weekly meetings and informal daily discussions from Years 1-5 in understanding the relationship between late life depression, chronic inflammation, and cardiovascular health.[70-74] Dr. Roose and I have already published together, and will continue to using data from NACC, NORA, as well as data from the present study.

2. INTERVENTIONS (Years 1-5): Adhering to the goal of designing and implementing interventions that personalize treatments based on refined assessment of patients with depression and frailty, I will develop methodological expertise in the design and execution of clinical trials in this population. To do so, I have designed a track with two components: a) *principles of clinical trial design and execution*, and b) *management and analysis of longitudinal data*. Although this study evaluates the implications of phenotype deconstruction for personalizing antidepressant treatment, the training in this track will be applicable for both future non-pharmacological and pharmacological interventions. This flexibility allows for the application of these principles to future intervention studies that will require the combination of treatment methodologies/modalities (e.g., exercise, cognitive behavioral, or pharmacological interventions) to personalize treatments and better serve these complex patients. Although I received advanced training in assessment and biostatistics in graduate school (including multiple regression, factor analysis, and structural equation modeling), this training was based on person-level data analysis, rather than person-period, longitudinal data and assessment of change.

1a) Clinical Trial Methodology: *Courses*: *Randomized Clinical Trial I (P8140), Randomized Clinical Trial II (P8142). Knowledge Acquisition Activities*: Reading tutorial will focus on select articles/chapters from Philip Lavori and Helena Kraemer on trial design and the assessment of the clinical impact of treatments. *Skills Acquisition Activities*: Patient recruitment for a clinical trial including advertising, the informed consent process, managing staff and logistics such as working with the pharmacy and research team to implement the protocol, and budgetary management. To increase practical training in the conduct of trial design, I will take an active role in my colleague Dr. Bret Rutherford's double-blind placebo-controlled trial investigating the mechanisms of the placebo effect (IRB #6308). I will conduct initial evaluations of depressed patients who respond to ads, weekly follow-up sessions, and assessments of frailty (at baseline and Week 8 prior to the breaking of the blind) on each of the older depressed patients who enter the protocol. Attend bimonthly Geriatric Psychiatry faculty meetings in which research methodological issues are presented. This forum provides practical experience in intervention design and confound-identification.

Advisory: **Steven P. Roose, MD** and I will have formal weekly meetings and informal daily discussions (his office is next to mine) on the intricacies of interventions research. Dr. Roose will provide expert guidance into interventions design and implementation, protocol creation and IRB review, the execution of protocols, staff and data management, patient recruitment, and budgetary administration. **J. Craig Nelson, MD** and I will have quarterly teleconferences along with Dr. Roose on the intricacies of intervention design with a particular focus on the design of future interventions based on the results from this project. Issues such as the design of an adequate control group for multimodal intervention projects and the issue of stratification in intervention designs will be discussed. Dr. Nelson will also add his expertise in the treatment of late-life depression to that

provided by Dr. Roose. Dr. Nelson, Dr. Roose, and I will meet annually at the AAGP conference, a tradition that will actually be a continuation from past conferences.

1b) Biostatistics: *Knowledge Acquisition - Courses*: *Applied Regression II (P8110), Generalized Linear Models (P8121), Longitudinal Data (P8157)*. *Skill Acquisition Activities:* Use of longitudinal data from a) the 2010 NACC Jr. Investigator Award, b) Dr. Maurer, c) NORA, as well as d) data collected during the award.

Advisory: **Sue Marcus, PhD**, and I will meet twice per month from Years 1-5, advising me in longitudinal data analytic methodology utilized in intervention work in conjunction with the courses above.

Training Evaluation: Throughout the project, Dr. Roose will provide me quarterly feedback based on reports from mentors and advisors. Dr. Roose will receive status updates from the mentor/advisor team on my progress within the *Skill Development Tracks*. I will complete a bimonthly status update on data analysis and manuscript submissions, ongoing collaborations, IRB issues, recruitment, and conference presentations and, in the latter stages of the *K23*, grant submissions. These reports will be matched against a yearly calendar that specifies a timetable for all goals, factoring in real life events such as births of children, thereby allowing for feasible task deadlines that balance personal/professional matters while maximizing productivity.

Table 1: Timeline Summarizing Training Activities and Integration with Research Activities

Development Tracks	Year 1	Year 2	Year 3	Year 4	Year 5
The Complex Geriatric Patient	Activities: *Readings* (Roose, Maurer, Fried, Butters); *Manuscript prep:* data from 1) Dr. Maurer, 2) NORA, 3) NACC; *Patient contact:* CRLE, ALLDC, Kendal; *Meetings* in CLRE, ALLDC,WHSI, Kendal	*Readings* (Roose, Maurer, Fried, Butters); *Manuscript prep:* data from 1) Dr. Maurer, 2) NORA, 3) NACC, 4) data from current proposal; *Patient contact:* CRLE, ALLDC, Kendal; *Meetings in* CLRE, ALLDC, WHASI, Kendal	*Readings* (Roose, Maurer, Fried, Butters); Consult on design of nonpharmacologic interventions; *Manuscript prep:* data from current proposal. *Patient contact:* CRLE, ALLDC, Kendal; *Grant applications:* R21, R34, and R01.	*Readings* (Roose, Maurer, Fried, Butters); *Manuscript prep:* using data collected from current proposal. *Patient contact:* ALLDC, Kendal; *Grant applications:* R21, R34, and R01 (including resubmissions).	
	Advisory: Dr. Mathew Maurer (1 hr/2wks) --->				
	Advisory: Dr. Linda Fried (1 hr/3mo) --->				
	Advisory: Dr. Steven Roose (1hr/wk) --->				
	Advisory: Dr. Meryl Butters (1hr/3mo) --->				
Interventions (*Biostatistics*)	Course: P8110 (*2hrs/wk for 4 months*) *Applied Regression II,* methods for analyzing repeated measurement data in medical research	Course: P8121 (*2hrs/wk for 4 months*) *Generalized Linear Models,* introduces asymptotic statistics including semiparametric models, and bootstrap techniques	Course: P8157(*2hrs/wk for 4 months*) *Analysis of Longitudinal Data,* longitudinal data including sample size calculation, and generalized linear, and mixed effects models		
	Activities: Analysis/manuscript submission using: NACC and NORA, Dr. Mauer data	Database management; Analysis of baseline data; manuscript prep from secondary data sources	Preliminary analysis of Acute phase treatment data; Stat. techniques used in R21, R34, and R01 applications.	Analysis of Acute and Follow-up Phase data for use in R21, R34, and R01 new/resubmitted applications.	
	Advisory: Dr. Sue Marcus (1hr/2wks) --->				
(*Clinical Trial Methodology*):	Readings: Determining treatment effect via trial design (Kraemer, Lavori): implications for Interventions methods	Course: P8140 (*2hrs/wk for 4 mo*) *Randomized clinical trial,* fundamental methods and concepts of the randomized clinical trial		Course: P8141 (*2hrs/wk for 4 mo*) *Randomized clinical trial II,* complex clinical trials continued	
	Activities: Patient enrollment in the ALLDC for the K23; Patient assessment for double-blind, placebo-controlled trial (#6308).		Managing research coordinator; working with the pharmacy to maintain protocol, manage budgetary issues; Placebo-control (#6308)		Complete f-up assessments
	Advisory Dr Steven Roose (*1hr/wk*) --->				
	Advisory: Dr. J. Craig Nelson (1hr/3mo) --->				
Ethics Track	Course: *Regulatory & Ethics Workshop, Irving Institute for Clinical and Translational Research,* (*1.5hr/mo*). Topics: capacity to consent & protecting human subjects.	Course: *Columbia University Ethics & Experimentation* (*2hrs/wk for 4 months*). Topics: historical, legal, theoretical and practical ethical research issues	Course: *NYSPI IRB Program for Junior Investigators* (*2hrs/mo; Years 3-5*). A program where junior investigators join an IRB subcommittee, shadowing an IRB member reviewing protocols.		
	Activities: Submit trial to Columbia IRB, recruit and enroll. Submit Year 2 continuation to Columbia IRB, maintain recruitment. Monitor budget.		Activities: Submit yearly continuation to Columbia IRB, maintain recruitment, follow-up assessments; take part in IRB via Jr. Investigator Program.		
	Advisor: Paul Appelbaum, MD (1hr/mo) --->				
General Education	Conferences: Annual American Association for Geriatric Psychiatry and Gerontology Society of American conferences; **General Educational seminars:** Geriatric Psychiatry Seminar (monthly), the Biostatistics Seminar (monthly), and Psychiatry Grand Rounds (Weekly).				
Total hrs per wk	8.75 hrs	10.75 hrs	8.75 hrs	6.75 hrs	5.75 hrs

Note. NORA: Nordic Research on Ageing; NACC: National Alzheimer's Coordinating Center; CRLE: Cardiovascular Research Laboratory for the Elderly; ALLDC: Adult and Late Life Depression Clinic; WHASI: Women's Health and Aging Study; Kendal: Kendal on Hudson, Sleepy Hollow, NY; NYSPI: New York State Psychiatric Institute.

5. *Training in the Responsible Conduct of Research*: An independent clinical investigator must conduct research with integrity and understand the ethical challenges of research, including conflicts of interest, human subject policies, collaborative research, and misconduct. A significant portion of my training will be devoted to the specific and complex issues that arise in clinical research involving the elderly such as laws and regulations concerning capacity to provide informed consent, particularly in the context of severe disability, psychiatric symptomatology, and cognitive impairment. This Skills Track combines didactics, monthly supervision with an Ethics advisor, discussions with Dr. Roose, a member of the IRB, totaling a *minimum* of 12-hours per year for the duration of the project. *Duration*: Yrs 1-5.

Courses: *Columbia's Irving Institute Regulatory and Ethics Workshop and Seminar on Law, Ethics, and Psychiatry; Columbia's Ethics & Experimentation*, and the *New York State Psychiatric Institute (NYSPI) IRB Program for Jr. Investigators*.
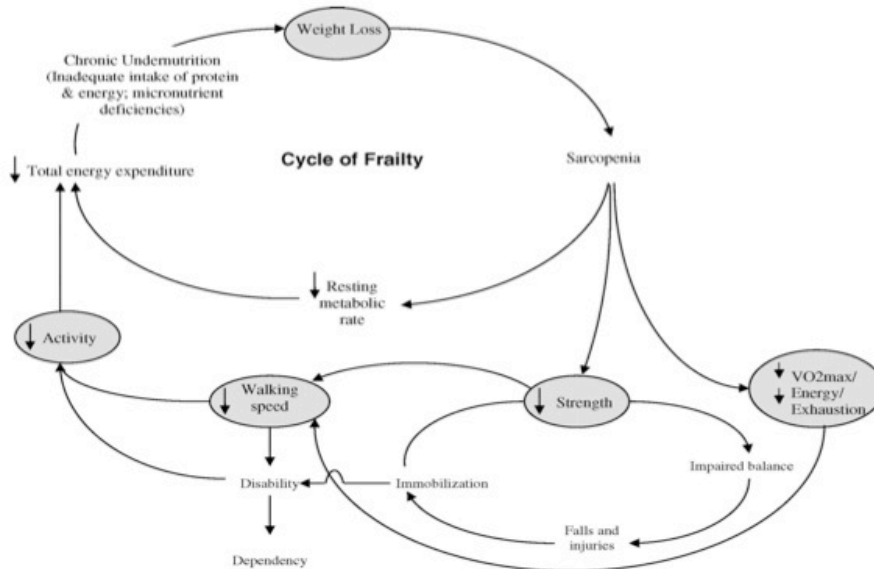
Advisory: **Paul Appelbaum, MD** and I will meet monthly for the duration of the award discussing the ethical and legal responsibilities for conducting research with elderly participants.

11. Research Strategy: Significance:

I. *Frailty is associated with greater morbidity and mortality*: Frailty is a syndrome marked by vulnerability that results from declines across multiple physiologic systems (Figure 1). The syndrome is defined by decreased strength, energy, and physical activity, slowed motor performance, and unintentional weight loss. These symptoms induce a self-perpetuating cycle of naturally progressing events[9-11,67] (Figure 1) that develop hierarchically with weakness emerging early in the process and weight loss and exhaustion representing a final pathway towards frailty.[11] The frailty syndrome is associated with greater depressive symptoms, cognitive impairment, and disability.[9,75,76] Three year follow-up data from the Women's Health and Aging Initiative[10] showed that the prefrail (1-2 characteristics) had more than a 5-fold higher risk of severe incident ADLs and nursing home entry, and 3-fold higher risk of death than nonfrail elders; the frail (> 3) had a 10-fold greater risk of incident ADL disability, 24-fold increased risk of nursing home placement, and 6-fold higher risk of death. These results indicate that 1) the prefrail and frail elders are living in the community, and 2) these community dwelling elders are at a "tipping point" towards dire outcomes. Thus, the syndrome of frailty is an important target for interventions.
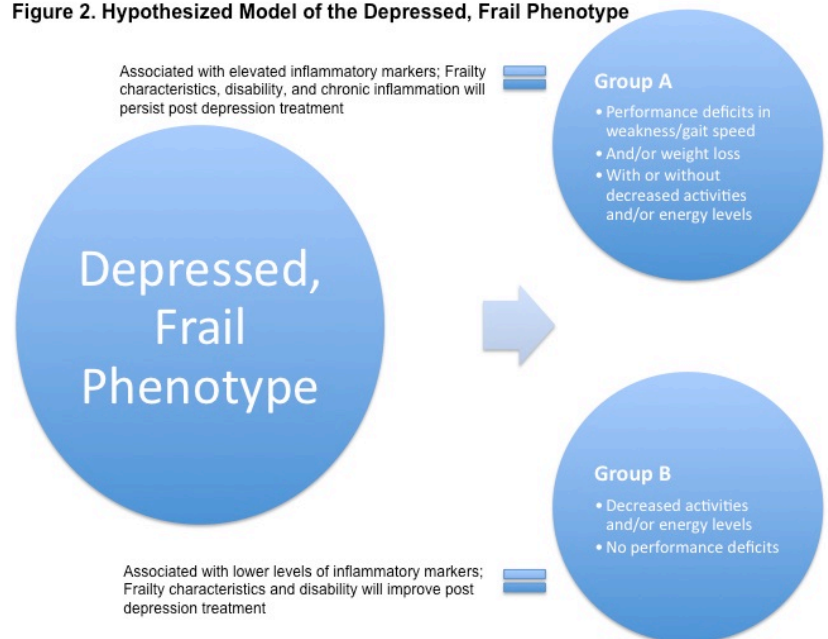

Figure 1. Cycle of frailty [adapted from Fried and Walston (9)].

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II. *The depressed, frail phenotype*: Frailty and depression are *phenomenologically* and *physiologically* associated. There are symptoms *common to both* late life depression (psychomotor slowing, weight loss, decreased activities, low energy) and frailty (low energy, decreased leisure activities, decreased walking speed, weight loss). The Cardiovascular Health Study[9] reported that the rate of depressive symptoms increased proportional to the number of frailty characteristics present: 16.2% of prefrail and 31% of frail elders had a CES-D > 10, compared to 2.6% of nonfrail older adults.[13] Additionally, 25.4% of the 1027 75-year olds recruited for the Nordic Research on Ageing study (see: **Pilot Data**) had significant depressive symptomatology (CES-D>16); these individuals demonstrated greater impairment in gait speed and grip strength, and had greater reported exhaustion and lower activity levels compared to nondepressed individuals. The association between depression and frailty may go beyond symptoms and include shared *physiological dysfunction*. Both depressive disorders and the syndrome of frailty are associated with chronic inflammation (increased levels of IL-6 and CRP)[16-23] as well as malnutrition.[24-28] More recently, researchers[66,77] identified that, among inflammatory diseases, depression was associated with a significant increase in risk for frailty. These findings emphasize the clinical importance of the depressed, frail phenotype, yet no clinical programs to date have been initiated to study this unmet need (NIH's RePORTER). This research program will advance scientific knowledge by using antidepressant medication to deconstruct the depressed, frail phenotype and will be the first step in a research career using comprehensive assessment to personalize therapeutic interventions for diagnostically complex geriatric patients.

III. *Conceptualizing the depressed, frail phenotype* (Figure 2): Depression and frailty in older adults share phenomenological and physiological profiles.[9,65,66,77] There are a number of possible models to explain the phenotype. First, the two conditions may be unrelated to each other but frequently coexist because they both occur at a higher rate in the elderly (as with cataracts and arthritis, for example). Second, one condition may be a risk factor for developing the other. In this model it is critical to know if the conditions occur in the same patient at different times and the sequence of the presentation of the two conditions, that is, whether their onset is concurrent or whether one generally precedes the other. Third, the relationship maybe an illusion and perhaps a misleading one; two disorders that appear to be distinct are really different manifestations of the same disorder.[78] For example, there is now evidence to suggest that depression is an early symptom of Huntington's disease rather than a separable diagnosis.[79]

In patients diagnosed as depressed and classified as prefrail due to deficits in energy level and decreased activities (Group B), I hypothesize that this classification is entirely congruent with the diagnosis of late life depression, and successful treatment of the depressive illness will result in improvement in frailty characteristics and in secondary domains such as disability. In patients diagnosed as depressed and classified as prefrail or frail with weakness, slowed gait speed, and/or weight loss (Group A), I hypothesize that the relationship between frailty and depression may be understood in two ways: 1) causally (being frail increases the risk of developing depression, or vice versa) or 2) as a manifestation of a unified geriatric syndrome with a common underlying pathophysiological mechanism such as chronic inflammation. In the latter instance, not only will Group A have elevated inflammatory markers at baseline, but also change in these markers may act as a surrogate for long-term outcome.[19-21,70-73] The critical difference between the two hypothesized manifestations of the phenotype is the presence of physical deficits in gait speed, grip strength, and/or weight loss in Group A; both groups may report decreased energy or activity levels, but I hypothesize that the presence of these physical deficits will predict worse response to antidepressant medication and greater long-term disability. By deconstructing this phenotype, I can uncover this potential heterogeneity and determine whether this heterogeneity effects response to depression treatments.

Figure 2. Hypothesized Model of the Depressed, Frail Phenotype

Associated with elevated inflammatory markers; Frailty characteristics, disability, and chronic inflammation will persist post depression treatment

Depressed, Frail Phenotype

Group A
- Performance deficits in weakness/gait speed
- And/or weight loss
- With or without decreased activities and/or energy levels

Group B
- Decreased activities and/or energy levels
- No performance deficits

Associated with lower levels of inflammatory markers; Frailty characteristics and disability will improve post depression treatment

Innovation:

I. *A Bridge Between Geriatric Medicine and Psychiatry*: Despite the *phenomenological* and *physiological* overlap between the two conditions, the frailty syndrome has remained a focus of study for geriatric medicine and outside the purview of psychiatry.[13] In the past 10 years, the *American Journal of Geriatric Psychiatry* has published only three articles[14,29,80] that included frailty in the title. Interestingly, one of those three articles[29] called for a multidisciplinary focus on depression and frailty, and described depression as a "psychosocial frailty," limiting a patient's resources to adequately deal with physical or social stressors. By neglecting to assess patients for frailty, geriatric psychiatrists may be overlooking clinical characteristics that predict treatment response similar to the way that presence of white matter hyperintensities, executive dysfunction and anxiety are associated with lower treatment response.[33,34,81] Thus the relationship that underlies the depressed, frail phenotype, as well as the optimal way to treat this population, has been unstudied in geriatric psychiatry.[13] In fact, recent epidemiological research shows that depression is a major risk factor for incident frailty 3 years after evaluation.[15] This project is innovative in that it represents the first step towards bridging the gap between geriatric medicine and psychiatry to foster a better understanding of diagnostically complex geriatric patients. Advances in assessment techniques can lead to better patient identification and the personalization of interventions to maximize treatment effectiveness and quality of life in complex geriatric patients. I propose to use an intervention to help define this clinical group. The approach will allow us to understand the dimensions of the depressed, frail phenotype that predict treatment course and outcome. By recruiting a multidisciplinary team of experts, I can combine the knowledge gained from geriatric psychiatry and medicine by utilizing a multifaceted approach to the phenomenological association between depression and frailty and begin a career focused on assessing and treating complex geriatric patients.

II. *Deconstructing the depressed, frail phenotype*: The complexity of this population requires a comprehensive approach to patient characterization. The deconstruction of the depressed, frail phenotype by identifying clinical characteristics that predict differential response to acute and long-term depression treatment adheres to the principles of the NIMH's Research Domain Criteria (RDoC) by classifying this phenotype across affective and cognitive systems and assessing treatment response using different units of analysis including dimensions of behavior, cognition, and neurobiological measures. In doing so, I am shifting the emphasis from

a classic symptom reduction model in unidimensionally diagnosed research samples to one based on multidisciplinary assessment of complex patients to enact comprehensive approaches to patient care.

Approach

I. Preliminary Data and Rationale for the Current Proposal:

1) High Risk Clinical Population: There are differences in progression to death based on the presentation of frailty characteristics and depression status. Using data from the Nordic Research on Ageing project, a longitudinal study of functional capacity in 75-year old community dwelling men and women, I found that older adults with slow gait speed and/or low grip strength (Group A) showed greater risk of death at baseline compared to individuals without these deficits. This effect on mortality is greater in depressed (OR = 2.11 [1.35-3.29]) compared to nondepressed (OR: 1.43 [1.09-1.88]) elders. Grip strength and/or gait speed deficits result in a 20% decrease in cumulative survival and an earlier time to mortality in depressed elders (right side; Figure 3) compared to the presence of the same characteristics in nondepressed elders (left side; Figure 3).


Figure 3. Cox proportion hazard models by frailty presentation and depression status

2) Depressed sample with frailty pilot data: The "Old-Old" study, a placebo-controlled trial (Columbia was lead site) of citalopram in depressed patients (N=164; 85 on Placebo, 79 on citalopram) with a mean age of 79.6 (SD = 4.5),[52] provides data from a sample that is similar to the sample that will be recruited for this current project: older depressed patients with moderate to severe medical illness burden (baseline mean total score of the Cumulative Illness Rating Scale – Geriatric, CIRS-G, of 7.2, SD=3.8). Using clinician-rated HRSD items (*psychomotor slowing, weight loss, decreased activities, decreased energy*) as a surrogate for frailty characteristics, I found that 163 of the 164 patients had $\geq$ 1 clinician-rated approximation of frailty characteristics (prefrailty=63, frailty=100), with 104 having psychomotor slowing and/or weight loss with or without decreased activity and/or energy (*Group A*) and 59 having decreased activity and/or energy but no slowing or weight loss (*Group B*). Following 8-weeks of treatment, there was no difference in antidepressant response between patients in Group A and Group B. Patients in Group A, however remained more frail post treatment (46% of the patients in Group A exhibited $\geq$ 3 frailty characteristics at Week 8 compared to 16.6% of patients in Group B) and more disabled post treatment (M_{diff} = 2.44 IADL pts) compared to patients in Group B. Thus, although patients in both groups respond to antidepressant treatment, patients with a physical performance manifestation of the frailty syndrome (Group A) remain significantly more frail and disabled post antidepressant treatment compared to patients in Group B.

Similarly, 23 of 24 older depressed patients whom I assessed in the ALLDC (IRB # 6470) met criteria for prefrailty (n=17) or frailty (n=7). Of these 23 patients who met for prefrailty or frailty, 7 had impaired grip strength, 5 impaired gait speed, 7 reported unintentional weight loss, 17 exhaustion, and 12 low activity levels. With respect to my hypothesized model, 15 had a Group A presentation (physical frailty deficits), and 8 presented consistent with Group B. 20 patients met study criteria and entered a treatment protocol: 16 met criteria for MDD and 4 met criteria for dysthymia. 10 met criteria for amnestic MCI. At the time of grant submission, 9 had completed 8 weeks of antidepressant medication treatment: 2 of 5 (40%) patients in Group A responded to antidepressant treatment compared to 4 of 4 (100%) patients in Group B. Remission rates (8-week HRSD < 10) were identical. At 8-weeks, 60% of patients (3 out of 5) with a Group A presentation at baseline met criteria for frailty (> 3 frailty characteristics), compared to 0 of 4 patients with a Group B presentation at baseline.

3) Feasibility and Tolerability: As the ALLDC pilot data and the Old-Old study demonstrate, recruiting a suitable sample of older depressed patients with characteristics of frailly is feasible. Another significant concern in the treatment of frail elders with antidepressants is safety and tolerability. The dropout rate for the Old-Old sample was 20% on drug vs. 14% on placebo and early termination due to an adverse event was 10.7% for drug vs. 1.1% for placebo (with no significant differences in rates of treatment emergent side effects). In the ALLDC (open label), none of the 20 patients treated in the clinic dropped out due to safety/tolerability issues.
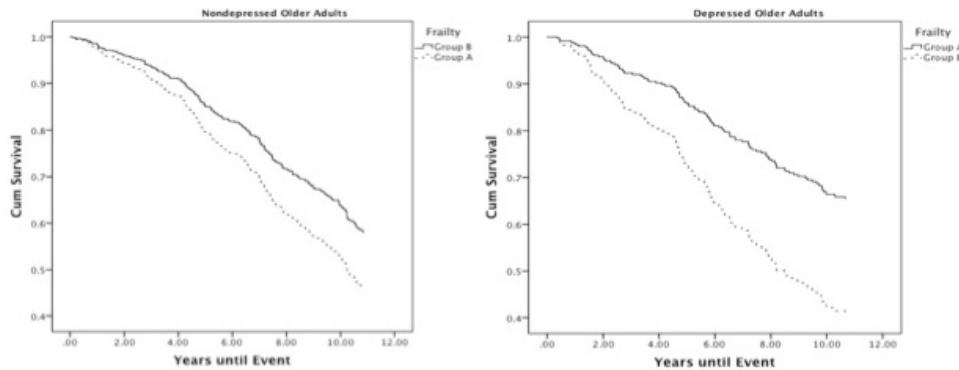
4) A New and Unique Long-term Research Project: I have established a relationship and begun a protocol (IRB #6608) with Kendal on Hudson, an independent living facility in Westchester, NY, in which I assess residents for characteristics of frailty and screen for depressive symptoms. Currently, I have recruited 80 residents, 45 of whom have been assessed. At one year following the assessment, prognostic information (changes in level of care, comorbid medical illnesses, falls, and death) will be collected. Currently, I am collaborating with members of my mentor/consultant team as well as the administration at Kendal to develop a program to prevent incident frailty characteristics and/or depression through a series of intervention protocols including exercise, nutrition, and the early diagnosis and treatment of depression. This ongoing research collaboration is based on a unique cohort, a nonclinical sample, which can support a future R01 application focused on the prevention of frailty and the promotion of successful aging.

Rationale: These data underscore the effect that baseline frailty characteristics has on 1) overall mortality, 2) treatment response to antidepressant medication, and 3) disability in older depressed frail patients. In fact, these data strongly suggest that when a geriatric psychiatrist assesses an older depressed patient, the patient will invariably meet criteria for, at minimum, prefrailty. **Ironically, the commonness of prefrailty may obscure the effect that the frailty syndrome has on treatment response and outcome in older depressed patients. The pilot data illustrate that the presence of deficits in psychomotor slowing/poor gait speed, poor grip strength, and/or weight loss (Group A) predicts 1) greater disability post depression treatment, 2) poorer response/remission, and 3) mortality.** Furthermore, these data establish that it is feasible to recruit, enroll, and treat a sample of older adults with a depressive disorder who meet criteria for prefrailty or frailty and that the use of antidepressant medication is safe and tolerable in a population similar to the one that will be recruited for this proposed research.

The project outlined in this K23 goes beyond the pilot data by classifying patients along multiple constructs, in particular the Cognitive (e.g. episodic memory, processing speed, and executive function) and Physical Systems (e.g. weakness via grip strength, lower extremity strength via gait speed and chair stand). This project is exemplary of the RDoC principles by measuring these constructs using multiple methods of analysis (including self-report, physiological, and behavioral data, most notably using actigraphy to measure change in activity level) and allows for the collection of data on the deconstruction of the depressed, frail phenotype. These data will result in the submission of future intervention protocols that personalize treatments for patients with specific presenting symptoms and characteristics.

II. Design Overview: 60 older adults (age $\geq$ 65) with a depressive disorder (DSM-IV diagnosis of dysthymia or Major Depression) and $\geq$ 1 frailty characteristic will be recruited to participate in an open-label trial of escitalopram or duloxetine in the ALLDC at the NYSPI. Recruitment will continue until a minimum of 30 patients with and without baseline deficits in grip strength, gait speed, and/or weight loss are enrolled to assure adequate power to find an effect between groups (i.e., a minimum of 30 patients with a Group A and 30 patients with a Group B presentation will be recruited). Patients will be enrolled into the Acute Phase and treated with escitalopram. Psychiatric, medical, neuropsychological, and functional assessments, blood work, vital signs and ECG with be conducted at baseline and repeated at Week 8; patients will be assessed weekly in the clinic for depressive symptomatology and adverse events (Table 2) during the Acute Phase. Because these patients

Table 2. Assessment Schedule for Repeated Measures		Acute Phase			Maintenance Phase		
	Evaluation	Baseline	Weekly	Week 8	Monthly	6-months	12-months
Frailty Assessment	X			X		X	X
Medical/Psychiatric Eval/Check	X	X		X	X	X	X
HRSD	X	X	X	X	X	X	X
Beck Depression/Anxiety		X		X		X	X
CGI-I		X	X	X	X	X	X
TESS		X	X	X	X	X	X
Functional Assessment		X		X		X	X
Neuropsych battery		X		X		X	X
Blood work		X		X		X	X

have a diagnosis of major depression or dysthymia, there is a responsibility to first and foremost ensure that patients achieve measurable improvement in depressive symptoms. For this reason, remission of symptoms (8-Week HRSD$\leq$10) is the clinical goal. If patients do not remit to the first pharmacologic trial at Week 8, patients will receive duloxetine and be followed weekly for a second 8-week Acute Phase trial. **All patients will continue into the Follow-up Phase.** Patients who remit to either of the Acute Phase trials will be maintained on their treatment regimen and followed monthly. Patients who do not remit to either Acute Phase trial will be

treated as clinically indicated (i.e. augmentation strategies, etc.) in the ALLDC during the Follow-up Phase. Dr. Roose (Primary Mentor) will be responsible for administering antidepressant treatment during both phases. During the Follow-up Phase, patients will have monthly assessments in the ALLDC, and full assessment batteries at 6- and 12-months (Table 2).

III. Inclusion/exclusion criteria (discussed in **Human Subjects**): *Inclusion criteria*: 1) Age $\geq$ 65, 2) DSM-IV diagnosis of Major Depression or Dysthymia and HRSD$\geq$16, 3) $\geq$ 1 frailty characteristic (Table 3), 4) willing and able to provide informed consent, 5) currently being followed by a Primary Care Physician, PCP, and willing to provide a release of information to facilitate communication between the study physician and PCP.
Exclusion criteria: 1) Acute cancer treatment, 2) acute or unstable medical illness, 3) end stage medical illness (e.g. liver, kidney, pulmonary) with high risk of mortality within 12-months, 4) Mini Mental State Exam $\leq$ 24, 5) diagnosis of dementia, 6) diagnosis of substance abuse or dependence (excluding nicotine) in the last 12 months, 7) history of psychosis or bipolar disorder, 8) significant risk of suicide, 9) failure to respond to adequate trial of escitalopram (at least 4 weeks at dose of 20 mg) and duloxetine (at least 4 weeks at dose of 90mg) in the current episode, 10) history of allergic or adverse reaction to escitalopram or duloxetine.

IV. Rationale for study design issues:

 A. *Why treat depressed, frail older adults with pharmacotherapy?* We debated the strengths and weaknesses of several potential interventions and designs that would allow for the deconstruction of the phenotype. The two major intervention options that were judged to have an acceptable balance of risk and potential benefit were exercise programs and antidepressant medication. ***Exercise alone***: An exercise intervention was considered due to its effectiveness in improving frailty characteristics in frail, nondepressed elders.[58,82-85] Research on the effectiveness of exercise on depression or depressive symptoms however is mixed[86,87] with a recent meta-analysis showing no statistical effect of exercise on depressive symptoms.[88,89] The dropout rate for the exercise group was nearly double that of the placebo group in one study of nondepressed, frail patients (34% vs. 18% respectively); this rate is likely to increase with the inclusion of depressed patients in the sample. Because of the substantive concerns about conducting an exercise trial in depressed patients, we felt that an exercise intervention was not the *optimal initial treatment* regimen for depressed, frail elders in this K23 study. ***Antidepressant medication***: Antidepressant medication was considered due to its effectiveness in treating depressive symptoms and the similarity between frailty characteristics and symptoms of late life depression. Although the use of antidepressant medication will allow us to deconstruct the depressed, frail phenotype, there are concerns over potential adverse events and attrition using an antidepressant in a frail older population. Special risks to the elderly involve sway (increased risk of falls), hyponatremia, and bleeding. Recently, an epidemiological study found that depressive symptoms and antidepressant users were at greater risk of incident frailty at 3-year follow-up. The incident frailty, however, cannot be definitively linked to the antidepressant use. As the authors correctly conclude, "antidepressant users, especially those still experiencing depressive symptoms, may suffer from a more-severe, recurrent, or chronic form of depression."[15] As shown in the pilot data,[52] we have found that the use of a selective serotonin reuptake inhibitor (SSRI) is feasible and tolerable in depressed patients over 75 years of age[52] with comorbid medical illness. Caution will also be taken, including systematic safety monitoring (Treatment Emergent Signs and Symptoms, TESS) by the treating psychiatrist at each visit, and the use of a conservative dosing schedule. Whereas there are potential risks, the potential benefit is an important consideration as well. We felt that the potential effectiveness and the proven feasibility of using antidepressants in this sample combined with the steps taken to mitigate risk, justifies this proposal. ***Combined Antidepressant and Exercise***: It is possible that combining exercise with antidepressants would be an optimal intervention for depressed, frail patients. Given that depression decreases the effectiveness of exercise interventions (and could potentially increase the attrition rate), it would be reasonable to implement the interventions sequentially. I submitted an R21 that proposed to test the feasibility of such a design, with the goal of assessing treatment efficacy. The reviewers felt that, although the project "could have a significant impact on the field" with "high public health significance", more preliminary data on the depressed frail phenotype was needed and, in order for me to execute such a study, I needed to acquire the very skills that I will learn in the Training Plan of this K23. Thus the summary statement from the R21 review indirectly points to the very goals of this K23 application, which are twofold: 1) To deconstruct the depressed, frail phenotype, and 2) to train in (a) the assessment and understanding of biological, neuropsychological and physical characteristics of complex geriatric patients, and (b) the design and conduct of interventions. Hence, given these goals, the use of a single treatment modality is most appropriate.

 B. *Why use an open-label trial design?* The major hypothesis of this study states that specific characteristics of the depressed-frail phenotype predict treatment outcome. We considered alternative trial designs to test this hypothesis: An *open-label trial* can test the hypothesis with fewer patients, but will be unable to determine

whether the observed effect is attributable to study medication or placebo response, or rater bias (lack of a blind). A *placebo-controlled trial* can also test the hypothesis and furthermore determine if the effect observed is attributable to group differences in response to placebo or study medication. A placebo-controlled trial, however, would require a sample size 2-3 x larger because of 1) the division of the sample into two cells (placebo vs. active medication), 2) the necessary stratification by frailty characteristics, and 3) the higher attrition rate in placebo-controlled designs. Thus, we concluded that due to these feasibility concerns and the absence of prior research on the depressed, frail phenotype, at this stage an open label protocol was most appropriate. The pilot data suggest that the presence of specific frailty characteristics, in particular impaired grip strength, gait speed, and/or weight loss, may predict treatment response. The goal of this study is to test this possibility and investigate the neuropsychological (episodic memory, processing speed, executive function) and physical (biological markers of inflammation and malnutrition) correlates for the differing manifestations of this phenotype. Therefore all patients will receive active treatment. If the results show, however, that antidepressant medication is beneficial for improving the severity of both depression and frailty regardless of deficits in specific baseline frailty characteristics, this is in and of itself important. Such a finding would suggest that antidepressant medication has beneficial properties for the syndrome of frailty, and thus a randomized, double-blind, placebo-controlled trial of antidepressants would be warranted to test this hypothesis. The interventions training that I receive in this K23 award will equip me to pursue these future directions by fostering the methodological skills and knowledge of the intricacies necessary to design and conduct future intervention protocols. Learning to treat geriatric patients pharmacologically and discussing these treatment decisions and the evidence base that supports them with my Interventions team of Drs. Roose and Nelson will greatly increase my knowledge of geriatric interventions and better inform the design of future intervention protocols. Additionally, my added role in an ongoing double blind placebo controlled trial (*mechanisms of the placebo response*: Rutherford - PI) will enhance my skills training in conducting more intricate intervention designs. Together, the training plan and protocol provide opportunities to develop the requisite skills and content base to establish a career investigating the phenomenology and treatment of medically complex geriatric patients with neuropsychiatric disorders.

  C. *Why age > 65?* The frailty syndrome is primarily a geriatric syndrome, and the incidence of frailty increases with age. Frail samples from recent studies had mean ages of 73.9 (SD = 2.8)[11] and 83 years (SD=4)[58].

  D. *Why the medical inclusion/exclusion criteria?* Recruiting a sample representative of patients with depression and frailty necessitates the inclusion of patients with a range of medical illnesses. While comorbidity will be included, those with acute (pneumonia) and/or unstable medical illness (recurrent episodes of pulmonary edema) are excluded because their participation would not be feasible.

  E. *Why 8-weeks for the Acute Phase?* Although it was traditionally believed that older adults respond more slowly than younger adults to antidepressant medication, more recent studies do not support this.[63] Additionally, because patients have a diagnosis of major depression or dysthymia, there is a responsibility to first and foremost ensure that patients achieve measurable improvement in depressive symptoms. Thus, remission of symptoms (HRSD$\leq$10) is the clinical goal. Patients who do not remit at Week 8 will be treated with an alternative antidepressant for a second 8-week Acute Phase trial. For these reasons, the length of the Acute Phase was deemed appropriate. A Follow-up Phase will allow for the investigation of change in secondary outcomes that may not show improvements during the Acute Phase (IADLs, mobility, etc.).

  F. *Why escitalopram and duloxetine?* SSRIs appear to have equivalent efficacy and side effect profiles in older adults.[63] There are however differences in pharmacokinetics and potential for drug-drug interactions, which is of special importance in geriatric populations and, specifically, this depressed, frail population.[90] Generic escitalopram has negligible effects on the cytochrome P450 hepatic system so the potential for drug-drug interactions is low. Duloxetine, a serotonin and norepinepherine reuptake inhibitor (SNRI)[91] was chosen over a 2nd SSRI or bupropion as it is safe and effective in geriatric populations.[92,93]

  G. *Why use the HRSD as the primary measure of depression?* HRSD is the most widely used outcome measure in studies of depression, including in late-life samples.[52,94-102] Because clinician-rated measures such as the HRSD can be prone to rater bias, the self-reported Beck Depression Inventory-II (BDI) will also be used.

  H. *Why assess cognition?* Cognitive impairment, specifically executive dysfunction, has been shown to attenuate response to antidepressant medication.[30,34] We have shown that impairment in episodic memory, executive function, and processing speed is associated with greater disability.[54] As such, we are proposing a brief but comprehensive battery to serially assess cognitive function for use as a covariate in the secondary analyses. These analyses will evaluate the effect of impairment in specific cognitive domains on the relationship between frailty characteristics and treatment response. The inclusion of MRI to assess white matter hyperintensities, although desirable, is beyond the financial scope of this K23 application.

V. Treatment Protocol:

  A. *Screening*: Patients will undergo a medical and psychiatric evaluation (including frailty characteristics) by a physician as part of the standard ALLDC evaluation (**IRB protocol # 5280R**).

  B. *Medication Washout*: If patients have been on an adequate dose of antidepressant medication for at least 12-weeks and are not responding (HRSD>14), a study physician will taper and stop the current medication (*washout period*). The patient will be off all antidepressants for 2 weeks (6 weeks if fluoxetine) and will be seen at least weekly by a study physician during the washout period. A washout period was included to maintain the fidelity of the assessment measures conducted at baseline. *Note*: patients who have previously failed trials of **both study medications** (escitalopram and duloxetine) are excluded from the study (see Exclusion Criteria).

  C. *Baseline evaluation*: Patients who meet study criteria at initial evaluation and provide informed consent to participate in the protocol will complete a 90-min baseline assessment prior to treatment initiation that includes 1) physical exam, 2) blood work, vital signs and ECG, 3) mood evaluation (HRSD, BDI,[103] Beck Anxiety Inventory [BAI][104], and anergia scale), 4) function evaluation (WHODAS2, ECog, SPPB; Baseline actigraphy ratings, obtained prior to treatment initiation), and 5) cognitive evaluation (Selective Reminding Task [SRT], Stroop Color-Word Interference Test, and Trail-Making Test Parts A & B). A psychiatrist will assess patients' side effect profiles using the TESS, and overall severity using Clinical Global Impression – Improvement (CGI-I) ratings. Because patients in this protocol may experience exhaustion, deceased energy and/or motivation, they can request a rest and will be asked if they need a break every 15 min. If necessary, sessions can be divided into 2 separate 45-min sessions. Between initial evaluation and baseline assessment (and every 3 months or as needed during the 12-month study), the study physician and PI will consult the patient's PCP to ensure well-coordinated patient care.

  D. *Dosing schedule and adjustment*: **Escitalopram**: 10 mg of escitalopram daily for first 4 weeks, and, if patients do not meet remission criteria (HRSD < 10), 20 mg daily for final 4 weeks. **Duloxetine**: If patients have previously failed a trial of escitalopram or do not meet response criteria at the end of an 8-week trial of escitalopram, they will be switched to duloxetine: 30 mg daily for the first week, then 60 mg for the next four weeks, and, if patients do not meet remission criteria, the dose is increased to 90 mg for the final three weeks. There is no known association between antidepressant treatment and increased suicidal risk in patients over age 24;[105] There appears, in fact, to be a decreased risk on antidepressants in adults aged 25-65, and a further risk reduction in adults > 65.[106] Patients considered at high suicide risk based on clinical assessment or with a history of recent suicide attempts are excluded. This protocol in this patient population has already received IRB approval (# 6470).

Table 3. Frailty criteria defined according to Fried et al., 2001				
Frailty criteria	**Definition for study inclusion**			
Shrinking	Unintentional 10 lb weight loss or 5% of previous year's body weight in last year.			
Weakness	Dominant hand grip strength as measured by a JAMAR dynamometer			
	BMI/male	Cutoff (kg)	BMI/female	Cutoff (kg)
	≤ 24	≤ 29	≤ 23	≤ 17
	24-26	≤ 30	23-26	≤ 17.3
	26-28	≤ 30	26-29	≤ 18
	> 28	≤ 32	> 29	≤ 21
Poor endurance	Self-reported exhaustion on two CES-D items: I felt that everything I did was an effort; I could not get going. Criterion is present if one was reported present for 3-days or more.			
Slowness	Low gait speed on 15′ walk at usual pace			
	Height/male (cm)	Cutoff (s)	Height/female (cm)	Cutoff (s)
	≤ 173	≥ 7 (0.65 m/s)	≤ 159	≥ 7 (0.65 m/s)
	> 173	≥ 6 (0.76 m/s)	> 159	≥ 6 (0.76 m/s)
Low activity	Evaluation of 18 activities from the Minnesota Leisure Time Physical Activity Questionnaire. Time spent on each is recorded in minutes for last 2 weeks, and multiplied by an activity score. Half of this represented in kilocalories represents weekly activity.			
	Male		Female	
	< 383 kcal/week		<270 kcal/week	

VI. Assessments (**Table 2**):

A. *Demographic information*: Patient demographics will be assessed during the initial evaluation. These include age, gender, education, race and ethnicity, and occupation.

  B. *Medical exam*: At initial evaluation and baseline, patients will receive a medical examination and the psychiatrist will document medical history including history of head injury, stroke, hypertension, cardiac disease, thyroid disease, other medical conditions, surgery, hospitalizations, and current medications. Medical comorbidity will be assessed using the CIRS-G. Tests will include CBC, chemistries and electrolytes, thyroid profile, vitamin B12 and folate levels, inflammatory and malnutrition markers (baseline, Week 8, 6- and 12-months), urine analysis, standing/supine systolic/diastolic BP, and ECG.

  C. *Psychiatric evaluation and diagnosis*: Psychiatric history, conducted during the initial evaluation, includes chief complaint, referral source, mood and cognitive decline (age-at-onset at both), family history of psychiatric illness, and alcohol/substance use. A trained rater will administer the SCID.

D. *Mood assessment*: The 24-item HRSD[41], administered by a trained rater blind to the treatment protocol, will be used to assess depression in this study; I will supplement the HRSD with the BDI.[103] CGI-I will be used for severity and improvement. A BAI[104] and anergia-scale[45,64] will be used to measure anxiety and anergia.

E. *Frailty assessment*: The frailty criteria (Table 3)[9,11,107] will be assessed at initial evaluation, Week 8, 6- and 12-months. Because patients with prefrailty (1-2 characteristics), a commonly targeted population in intervention studies of frail elders, are included,[58,59,61,107] I will assess both change in total number of frailty characteristics and change in severity of each specific characteristic as part of Hypothesis 2.

F. *Function/Disability assessment*: Domains of function assessed at baseline, 8-week, 6- and 12-months will include: 1) *mobility* via the SPPB[42], a performance measure of gait speed, balance, and lower extremity strength sensitive to meaningful change; *Social/physical function* via the 36-item self-report WHODAS2[43]. *Cognitively mediated function* will be assessed by the self-report 38-item ECog[44], adopted from an informant-report version. *Activity Levels* will be assessed using GT3X+ Activity Monitors from Actigraph.

G. *Neuropsychological assessment*: The battery assesses specific cognitive domains known to be associated with disability and/or predict treatment response. **Global cognition** will be assessed using the 30-item MMSE[108], a brief, structured mental status examination. **Episodic memory** will be assessed by the 12-item, 6-trial SRT[109] a widely used measure of list learning and memory. **Executive function** will be assessed via the Stroop Color-Word Interference Test[110], and Trail-Making Test-Part B.[111] **Attention and psychomotor speed** will be assessed with the Trail-Making Test – Part A.[111]

VII. Statistical Analyses:

The data analyses utilize linear mixed effects regression since this approach can handle missing data and the correlation of repeated measurements within the individual. Mixed effects models using maximum likelihood estimation provide valid inferences in the presence of ignorable nonresponse.[112] I will be trained by Dr. Marcus to use Supermix software written by Donald Hedeker and Robert Gibbons for the analysis of longitudinal data using mixed-effects linear regression.[113] To test Hypothesis 1, I will use linear mixed effects regression of depression score across time as a function of frailty deficit group (those with specific frailty deficits=1, those without specific deficits=0), 3 time dummy variables (time1=1 for week 8 and 0 otherwise, time2=1 for 6 months and 0 otherwise and time3=1 for 12 months and 0 otherwise) and the interaction of group by time dummies, with a random effect for repeated measures within the individual. I will use a contrast within this model to estimate and test the significance of the difference in outcomes between those with and without deficits at the end of the Acute Phase (8 or 16 weeks). Hypotheses 2 (outcome: total frailty characteristics) and 3 (outcomes: WHODAS2.0, SPPB, ECog, actigraphy scores; IL-6, CRP, serum albumin levels) will be tested in a similar way. The contrasts to test Hypothesis 3 will evaluate the deficit vs. non-deficit differences at 6 months and at 12 months. Secondary analyses will include reconducting the primary analyses with the inclusion of the total score on each of the three neuropsychological tests as a covariate. Actigraphy will be analyzed as the average 6-day energy expenditure level (total counts in kcal per day assessed over 8 days with partial first day and last day assessments discarded) between baseline and evaluation, Week 7-Week 8, and 8-day periods at 6- and 12-months based on the combination of the Work-Energy Theorem and the Freedson Equation to adjust for lower caloric expenditures if necessary. 60-second epoch will be used. Percentage of time spent as sedentary vs. moderately active will also be explored.

The power analysis for Aim 1 and Aim 2 is based upon the calculations for longitudinal models provided by Hedeker and colleagues,[114] with 4-time points assumed (0, 8 weeks, 6 months and 12 months) for the trend line. A two-group design and a random-effects structure with random slope, residual term and autocorrelated residuals, ICC=0.3 and a 10% attrition rate[115,116] between each pair of assessments are assumed. Tests are 2-tailed with α = .05. To test a between groups linear trend effect, 30 subjects per group at baseline will provide sufficient power to test for a moderate effect (between groups difference increasing linearly from 0 at baseline to .63 SD units). I recognize the limitations of using pilot studies to guide power calculations for a future R01. The proposed study however will be sufficiently powered to determine whether the effect size is clinically meaningful,[117] i.e. an effect size that is somewhat larger than moderate is likely to be clinically meaningful.