11. RESEARCH STRATEGY
11.1 Significance

Depressive disorders affect approximately 10% of the population in the United States annually with a lifetime prevalence of 10% in men and 15% in women. Along with the high prevalence, the costs associated with depressive disorders have also grown. The annual economic burden of depressive disorders is estimated at $83 billion and depressive disorders are predicted to be the greatest contributor to global health burden by the year 2030. Even among individuals who do not meet diagnostic criteria for Major Depressive Disorder (MDD), depressive symptoms have negative influences on health. Elevated depressive symptoms are associated with an increased risk of MDD, functional impairment, higher rates of disability, and increased social dysfunction. Further increasing the burden of depressive disorders is the limited accessibility and effectiveness of treatments. Only 55% of people afflicted with a depressive disorder are receiving treatment, while alleviation of depressive symptoms is seen in only 32% of those receiving treatment. Even with optimal access and treatment, data indicate only 34% of disability associated with depression would be averted. These data highlight the public health burden of depressive disorders and the need for implementation of strategies to prevent depressive disorders.

The Institute of Medicine and the National Institute of Mental Health have each produced reports calling for major efforts to develop, evaluate, and implement prevention interventions focused on mental, emotional, and behavioral disorders. The IOM paradigm for preventive interventions includes “selective” interventions, which target at-risk individuals that are not yet symptomatic. It has been argued that the use of selective interventions to prevent depression in medical illness should be prioritized. Selective prevention interventions targeting medically ill populations, such as post-stroke and macular degeneration patients, have been efficacious in preventing the incidence of depression. The proposed research involves a selective intervention aimed at preventing depression among Hepatitis C (HPC) patients receiving Interferon-α (IFN-α) treatment.

IFN-α is an efficacious treatment for HPC; however, IFN-α treatment results in a significant increase in depressive symptoms, with between 30-50% of patients developing MDD. In one of the largest prospective studies of HPC patients receiving IFN-α treatment, 39% of patients experienced moderate to severe levels of depression. This increased depressive symptomatology in HPC patients is associated with significantly impaired quality of life, reduced IFN-α treatment adherence, and poorer IFN-α treatment outcomes. This is in addition to the burdens typically associated with elevated depressive symptoms, such as functional impairment, higher rates of disability, and increased social dysfunction. Given the high risk of increased depressive symptoms during IFN-α treatment and the effects this increase in depressive symptomatology has on treatment adherence, treatment outcomes and patient quality of life, it is important to identify effective strategies for preventing the development of depressive symptoms in this population.

To date, research has focused on the prophylactic use of selective serotonin reuptake inhibitors (SSRIs) in the prevention of IFN-α induced depression in HPC patients. Open label trials suggest that the administration of SSRIs may reduce the incidence of depression during IFN-α treatment. However, out of four randomized controlled trials (RCTs), only one trial has shown a significantly lower rate of MDD in patients receiving SSRIs compared to those receiving placebo. Furthermore, SSRI treatment did not result in improved adherence to IFN-α treatment compared to placebo. In addition to these results, it has been postulated that non-depressed patients might be resistant to taking SSRIs, therefore non-pharmacological interventions may be more suitable for prevention. Taken as a whole, this indicates the need for alternative strategies for the prevention of IFN-α-induced depression.

Within the HPC population, the successful completion of this project offers several potential benefits. First, the prevention of IFN-α induced depression will eliminate the physical, psychosocial and economic burdens often associated with depression. Additionally, the successful implementation of an exercise intervention during IFN-α therapy may have the potential to improve treatment adherence and outcomes. Considering the reduced treatment adherence associated with depression, prevention of depression is likely to improve adherence to IFN-α therapy, thus improving treatment outcomes. Furthermore, it has been postulated that weight loss and increased of insulin sensitivity associated with exercise may be especially beneficial for patients with HPC.

Perhaps more importantly, the examination of exercise in the prevention of interferon-induced MDD has implications beyond the HPC population. MDD is a heterogeneous disease and it has been postulated that the biological underpinnings of MDD are equally varied. As a result, there are likely multiple biological targets for the prevention and treatment of MDD and therefore, multiple treatment options are likely necessary to...
effective treat and prevent MDD. Inflammation has been implicated in the development MDD and inflammatory responses to SSRI treatment may provide insights into inadequacy of current MDD treatments. Patients with a history of non-response to SSRIs have elevated levels of IL-6.\textsuperscript{70} Similarly, elevated baseline inflammation is predictive of non-response to a variety of depressive treatments.\textsuperscript{71-73} The model of IFN-\(\alpha\)-induced depression provides strong evidence for the role of inflammation in the development of MDD.\textsuperscript{74} Completion of the proposed project will provide further insight into the role of inflammation in the etiology of MDD, while also exploring the role of exercise as a treatment option for MDD patients with elevated systemic inflammation. Furthermore, several medical illnesses are associated with an increased risk of depression.\textsuperscript{75} This increased co-morbidity may be at least partially explained by elevated inflammation associated with these medical illnesses.\textsuperscript{76} If exercise proves to be efficacious in preventing depression in HPC patients, the results may be generalizable to other medically ill groups.

11.2 Innovation

The proposed project presents a novel strategy for preventing the incidence of depression in HPC patients receiving IFN-\(\alpha\) therapy. The potential of an exercise intervention to prevent depression during IFN-\(\alpha\) treatment is supported by longitudinal data demonstrating that physical activity reduces future risk of depression.\textsuperscript{77,78} Furthermore, exercise is efficacious as a stand-alone and/or adjunctive treatment for depression.\textsuperscript{2,7,79} The potential for exercise to prevent the increase of depressive symptoms in HPC patients receiving IFN-\(\alpha\) treatment is also biologically plausible. Examination of the mechanisms responsible for the development of IFN-\(\alpha\)-induced depression provides insight into potential prevention strategies. IFN-\(\alpha\) treatment increases peripheral levels of several proinflammatory cytokines, including increases interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)),\textsuperscript{80} and several studies have reported associations between increases in these cytokines and increases in depressive symptoms.\textsuperscript{74,81-84} Prather et al.\textsuperscript{85} examined the temporal relationships between IFN-\(\alpha\) treatment, IL-6, sleep disturbances and depressive symptoms in a cohort of non-depressed HPC patients receiving IFN-\(\alpha\) treatment. They report increases in IL-6 predicted higher depressive symptoms the following month and higher depressive symptoms predicted with higher levels of IL-6 the following month.\textsuperscript{74} This suggests a positive feedback system resulting in increases in IL-6 and depressive symptoms following IFN-\(\alpha\) treatment. Furthermore, the relationship between IL-6 and depression was mediated by changes in sleep quality, with increases of IL-6 predicting a worsening of sleep quality and the worsening of sleep quality predicting an increase in depressive symptoms (see Figure 1).

Figure 1. IFN-induced depression model proposed by Prather et al.: This model of IFN-\(\alpha\)-induced depression suggests that an intervention that decreases inflammation and/or improves sleep quality may be effective in preventing IFN-\(\alpha\)-induced depression. Higher levels of physical activity and physical fitness are associated with lower levels of IL-6,\textsuperscript{5,86} while exercise interventions have been shown to reduce inflammatory cytokines.\textsuperscript{87,88} Similarly, exercise improves various aspects of sleep quality in individuals with sleep complaints\textsuperscript{89,90} and in individuals with depression.\textsuperscript{91,92} Therefore, it is plausible that exercise may prevent an increase in inflammation and worsening of sleep quality during IFN-\(\alpha\) treatment and ultimately lead to the prevention of IFN-\(\alpha\)-induced depression.

My previous work further supports exercise as a potential strategy to prevent IFN-\(\alpha\)-induced depression. First, in a cross-sectional analysis of primary care patients, we report physical activity moderates the relationship between inflammation and depressive symptoms.\textsuperscript{5} In this sample, elevated levels of IL-6 were associated with elevated depressive symptoms among individuals who did not engage in regular physical activity, however there was no relationship between IL-6 and depressive symptoms among active individuals. This would suggest that physical activity may “protect” against the development of depressive symptoms in the presence of inflammation. Next, we examined pro-inflammatory cytokines as predictors of antidepressant response to exercise in patients with non-remitted MDD.\textsuperscript{11} We found higher baseline levels of TNF-\(\alpha\) were associated with greater decreases in depressive symptoms following an exercise intervention. This is in contrast to studies that report lower inflammation predicts treatment response to SSRIs.\textsuperscript{71,93} This would support the use of exercise in the current study, given the elevated inflammation resulting from from IFN-\(\alpha\) and the apparent inefficacy of SSRIs to prevent the development of MDD in HPC patients receiving INF-\(\alpha\) therapy. Finally, in the same sample, we found improvements in self-reported sleep quality following the
exercise intervention. \(^{10}\) Again, this is in contrast to previous reports of residual sleep disturbances following SSRI treatment.\(^{94-96}\) Taken as whole, this line of research would suggest that the mechanisms responsible for the antidepressant effects of exercise likely differ from the mechanisms of SSRIs and suggest that exercise may be efficacious in the prevention of IFN-\(\alpha\) induced MDD.

The proposed project is a novel application of an exercise intervention and therefore, no research in humans is available on the effects of exercise on the development of depression during IFN-\(\alpha\) treatment. However, animal models provide further support of the hypothesis. In a study of rats, concurrent treadmill running protected against the development of neurocognitive deficits during IFN-\(\alpha\) administration.\(^{97}\) In summary, this previous research supports the plausibility of exercise in the prevention of IFN-\(\alpha\) induced depression.

### 11.3 Approach

#### Previous Work

The proposed research is a logical extension of my previous work examining the effects of exercise on mental health. In addition to the work cited above, I have completed two meta-analyses examining the antidepressant and anxiolytic effects of exercise.\(^{1,2}\) The results of these analyses indicate that exercise interventions are efficacious in reducing depressive and anxious symptoms. The completion of these analyses also provided the opportunity to familiarize myself with past research examining the effects of exercise on mental health, while also identifying important areas for future research. Based on these efforts, I next focused on the identification of individual differences in depression and responses to exercise treatment. I conducted a randomized controlled trial of healthy college students to examine the moderating effect of the 5-HTTLPR genotype on changes in depressive symptoms following exercise. This work resulted in two publications, the first is a cross-sectional examination of the moderating effect of physical activity on the relationship between serotonin transporter genotype (5-HTTLPR) and depressive symptoms and the second manuscript examines the efficacy of a 5-week exercise intervention in alleviating depressive symptoms and the moderating effect of 5-HTTLPR genotype.\(^{4}\) I have also co-authored a paper from the Treatment with Exercise Augmentation for Depression (TREAD) study on the effects of brain derived neurotrophic factor (BDNF) on exercise augmentation of MDD.\(^{12}\)

The gaps in my research experience are complemented by the expertise of my proposed mentors and consultants. Dr. Madhukar Trivedi will serve as my primary mentor during the training period. Dr. Trivedi has extensive experience in the design and conduct of multi-site trials in depression. He served as the Co-Director of the National Coordinating Center in the multi-site trial of treatment-resistant depression, Sequenced Treatment Alternatives to Relieve Depression (STAR*D).\(^{16-19}\) Additionally, Dr. Trivedi has been a principal investigator in multiple clinical trials funded through NIMH, including the currently funded Establishing Moderators/Biomarkers of Antidepressant Response (EMBARC; 1U01MH092221). Of particular relevance to the proposed project, Dr. Trivedi is the principal investigator of two controlled trials examining the use of exercise in mental health and substance use, Treatment with Exercise Augmentation for Depression (TREAD)\(^{7}\) and Stimulant Reduction Intervention using Dosed Exercise (STRIDE).\(^{5}\)

Dr. Steve Blair, Professor of Exercise Science and Epidemiology at the University of South Carolina will provide additional mentorship in the implementation of exercise interventions in clinical populations. Dr. Blair has extensive experience in conducting RCTs using exercise interventions in clinical populations, including the Dose-Response to Exercise in Women (DREW; HL66262, Blair PI).\(^{20-22}\) DREW was an RCT designed to examine the effect of three doses of aerobic exercise on cardiorespiratory fitness and blood pressure in overweight or obese post-menopausal women with elevated blood pressure. Results of DREW identified a dose-response relationship between exercise dose and improvements in cardiorespiratory fitness. Dr. Blair also has been the PI on four other NIH-funded RCTs. His RCTs have included >1200 adult women and men aged 20-89 years and of numerous racial/ethnic groups. Dr. Blair served as an investigator for TREAD and is currently a consultant for STRIDE.

Dr. William Lee will serve as a consultant for the proposed project. Dr. Lee is the Director of the Clinical Center for Liver Diseases at UT-Southwestern, and leads large clinical trials of the treatment of Hepatitis B and C\(^{27-29}\) and was the founding Principal Investigator for the Acute Liver Failure Study Group (5U01DK058369).\(^{30}\) Dr. Lee will provide expertise in conducting clinical research in the HPC population and will also help facilitate recruitment of participants from the UT-Southwestern Clinical Center for Liver Diseases.

Dr. Ryan Huebinger will serve as a consultant for the proposed project. Dr. Huebinger is an instructor in the Department of Surgery at UT-Southwestern. Dr. Huebinger’s work is focused on the examination of biomarkers and genetic variants as they relate to clinical outcomes.\(^{31,32}\) Dr. Huebinger will to offer advice on the proper methods for sample collection and oversee the analysis of samples for inflammatory makers. Dr.
Huebinger conducted analyses of BDNF and inflammatory cytokines on blood samples collected during TREAD.\textsuperscript{11,12}

Participants
Individuals who have been diagnosed with HPC and prescribed IFN-\(\alpha\) will be recruited from the UTSW Clinical Center for Liver Diseases. Adults, ages 18-65, will be included. Participants will provide written informed consent before any protocol-specified procedures are carried out. Participants must receive medical clearance to exercise with protocol-defined stress testing (in accordance with American College of Sports Medicine (ACSM) guidelines) from protocol approved medical personnel. Individuals will be excluded from participation if they: 1) have a medical condition contraindicating exercise participation, 2) are currently physically active – defined as moderate intensity physical activity on 3 or more days per week for the last month, 3) have been diagnosed with current MDD or are currently receiving antidepressant medication treatment (including SSRIs and SNRIs) 4) suicidality, 5) current psychotic disorder.

Screening
Mini International Neuropsychiatric Interview (MINI). The MINI\textsuperscript{98} is a structured diagnostic interview designed to screen for Axis I psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 4th ed) and International Classification of Diseases (ICD-10, 10th ed).\textsuperscript{99} In comparison to the Structured Clinical Interview for DSM-IV Disorders (SCID-P), kappa values are good (only one diagnosis < .50), specificities and negative predictive values are .85 or higher across diagnoses, and in general, sensitivity is .70 or higher.\textsuperscript{99} The MINI is being used to ensure standardized psychiatric diagnoses. The MINI will be administered at the screening visit and will be used to identify Axis I psychiatric diagnoses.

Prior and Concomitant Medications. The Prior and Concomitant Medications form assesses prescribed medications taken by the participant. The Prior and Concomitant Medications form will be administered at the screening visit and then monthly thereafter, if the participant endorses a change in medication status.

Physical Activity Readiness Questionnaire-Revised (PAR-Q). The PAR-Q\textsuperscript{100} asks 7 health-related questions to determine whether a person needs to consult with their physician prior to engaging in an exercise program. The PAR-Q will be administered at the screening visit.

Physical Exam/ Medical History. A physical exam will be conducted for all participants to provide clearance for exercise. The medical personnel conducting the exam will review the participant's medical history. The medical personnel will also evaluate results from the medical exam, maximal testing and lab results, and will determine whether the participant is medically cleared to exercise.

Maximal Exercise Testing. Maximal exercise testing will be conducted during the screening process to examine cardiorespiratory responses in order to rule out ischemic response to exercise (with its implications of cardiovascular disease), to identify participants for whom exercise might be hazardous, and to provide data for the exercise prescription. A trained technician will process the test data and a report will be generated that contains the following information: 1) participant's symptoms before, during and after testing, 2) maximal heart rate achieved and percent of predicted maximal heart rate achieved, 3) time on treadmill and estimated maximal metabolic equivalent (METS) achieved, and 4) ECG interpretation. Identification of symptoms or conditions that require the test be stopped (based on ACSM's Guidelines for Exercise Testing and Prescription) will result in discontinuation of the test, as well as ineligibility for participation in the study. The test may be rescheduled and/or repeated in the event of equipment difficulty or failure, the failure of the participant to achieve their age-predicted maximal heart rate, or other situations determined by the testing and/or medical personnel to warrant a rescheduling of the test.

Measures/Assessments
Quick Inventory of Depressive Symptomatology - Clinician Rated (QIDS-C\textsubscript{16}). The QIDS-C\textsubscript{16}\textsuperscript{101-103} is a 16-item version of the 30-item Inventory of Depressive Symptomatology (IDS) designed to assess severity of depression-specific symptoms. Scores range from 0 to 27 with higher scores representing greater severity of depressive symptoms. The QIDS has been used in a number of major trials such as STAR*D. The QIDS-C\textsubscript{16} has high reliability (Cronbach's alpha of 0.90), good concurrent validity (correlations between the QIDS-C\textsubscript{16} and the 17-item Hamilton Rating Scale for Depression ranging between .86 and .93), and good inter-rater reliability (kappa of .85)\textsuperscript{101}. The QIDS-C\textsubscript{16} will be administered at baseline, every 2 weeks for the first 6 weeks and every 4 weeks thereafter by a blinded rater.

Pittsburgh Sleep Quality Index (PSQI). The PSQI\textsuperscript{104} is a 19-item scale designed to assess sleep quality and disturbances. Scores range from 0 to 21 with higher scores representing worse sleep quality. The PSQI has demonstrated reliability (Cronbach's alpha of 0.80) in the assessment of self-reported sleep quality and
validity when compared to sleep diaries and polysomnography. The PSQI will be administered at baseline, every 2 weeks for the first 6 weeks and every 4 weeks thereafter by a blinded rater.

Inflammatory markers. Blood samples will be obtained at baseline, Week 3 and subsequently every four weeks. Samples will be frozen at −80 °C until the time of analysis. Samples will be analyzed using a multiplexed ELISA method (Meso Scale Discovery) for IL-1beta, IL-6, IL-10 and TNF-alpha.

Accelerometers. Participants in both interventions will wear Actigraph GT3X+ accelerometers for 7 days in Weeks 1, 7, 15, and 23. Accelerometer data will be used to monitor physical activity outside of the intervention and to provide an objective measure of sleep quality. Accelerometers provide valid and reliable data on both physical activity and sleep quality.

### Assessment Schedule

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<th>Screening</th>
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<th>Week 3</th>
<th>Week 5</th>
<th>Week 7</th>
<th>Week 11</th>
<th>Week 15</th>
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### Intervention

50 participants will be randomly assigned to either: 1) exercise intervention or 2) health education control group for 26 weeks. Randomization will occur 2 weeks prior to initiation of IFN-α treatment.

**Exercise (EX).** Participants randomized to the EX condition will complete an exercise dose of 12 kilocalories per kilogram of bodyweight per week (KKW). The 12 KKW dose will result in approximately 120 minutes of exercise per week. All exercise sessions will be conducted in the Exercise Lab located in the UT-Southwestern Mood Disorders Research Program and Clinic and will be supervised by a trained exercise facilitator. The weekly exercise dose will be divided between at least 3 sessions, with additional sessions (up to two) completed as needed to achieve the target exercise dose and to allow for participants to develop autonomy in completing sessions. The exercise dose that was selected (12 KKW) is similar to doses shown to be efficacious in the treatment of major depressive disorder. In order to improve tolerability, the dose will be ramped so that participants achieve 6 KKW the first week, 9 KKW the second week, and 12 KKW in the third and subsequent weeks. Exercise intensity will be fixed to a range consistent with moderately high to high intensity, but will also be ramped up gradually in order to increase tolerability for participants; 50-60% maximal heart rate (HR\text{max}) during the first week 60-70% maximal heart rate (HR\text{max}) during the second week and 70-85% HR\text{max} for the third week and beyond. The ramping procedure proposed has successfully been implemented in the STRIDE study. Quantification of this range will be based on each participant's maximal heart rate as determined during maximal exercise testing at screening. Participants will wear a heart rate monitor throughout the exercise session and the exercise facilitator will monitor heart rate. The participants will warm up for 5 minutes (0 grade and 50-70% of speed) prior to initiation of the exercise prescription. Blood pressure will be assessed after 5 minutes of exercise. The exercise session will be halted if an extreme elevation in blood pressure is observed. The speed and/or grade can be adjusted to maintain the heart rate at a safe exercising level within the desired range. After completion of the exercise prescription, the participant will cool down (0 grade and 50-70% of speed) until their heart rate returns to within 15% of their resting heart rate. Following cool down, the participant will be led through 5-10 minutes of stretching.

**Health Education (HE).** Participants randomized to the HE condition will attend 3 sessions per week during which educational items such readings, websites, and audio and video materials will be viewed by participants and facilitators will instruct participants to log the materials reviewed. Instructional topics include areas such as healthy eating habits, recipes for healthy eating, preventive health care and recommended health screenings (e.g., cancer prevention, cardiovascular disease prevention), accessing health care resources, and other health related topics that are relevant to adults. Participants will be encouraged to suggest topics of interest to help maintain their involvement and engagement in the sessions throughout the duration of the study. The HE program is similar to a health education intervention currently used as an attentional control group in STRIDE, which was modeled after similar programs developed by Marcus et al (1999) and Rejeski et al (2005) that have been used successfully as control groups in clinical trials examining exercise as an intervention (Marcus et al, 1999; LIFE Study Investigators, 2006).
Recruitment of participants will begin in July 2013, with a recruitment goal of 2 participants per month. At this rate, recruitment will end in June 2015 and the last intervention sessions and assessment visits will occur in December 2015.

Analysis

Based on recommendations of Leon et al., Aims 1 and 2 of the proposed pilot study examine the feasibility of conducting an exercise intervention in patients undergoing IFN-α treatment. The feasibility of the study will be assessed by the following criteria:

1) Screening - the number of participants screened per month
2) Recruitment - the percentage of screened participants that are ultimately randomized
3) Intervention Adherence – defined as percentage of weekly exercise dose completed by participants randomized to the exercise condition.
4) Retention – defined as percentage of assessments completed

The data collected related to these criteria will be used as the basis for a subsequent R01 application proposing an RCT sufficiently powered to examine the efficacy of an exercise intervention in the prevention of IFN-α-induced depression. Outcomes related to screening and randomization will inform the proposed timeline and provide estimates for the number of clinical sites required to complete an adequately powered trial. Data related to exercise adherence and participant retention will inform alterations made to study procedures to address any difficulties encountered related to adherence and retention.

Consistent with Aim 3, we will conduct a data analysis examining the efficacy of the exercise intervention in preventing the increase of depressive symptoms during IFN-α treatment. A mixed-effects repeated measures model will be used to analyze the primary outcome measure, QIDS-C total score. The independent variables in the model will be time (weeks 3, 5, 7, 11, 15, 19, 23, 27)(within-subjects factor), treatment group (EX, HE)(between-subjects factor), and treatment group by time interaction. The model will allow for random slopes and intercepts while all other factors will be fixed effects. The baseline value of the dependent variable (QIDS-C) will be included as a covariate as will the other potential covariates if needed [age, race, gender, history of depression]. The need for higher order time terms or the transformation log(time+1) to obtain a better fitting model will be considered. The goodness of fit of the final model will be investigated. The analysis will use all available data from all randomized patients with at least one post-baseline visit (i.e., modified “intent to treat” sample) and all tests will be two-sided with alpha of .05 used for significance. The hypothesis will be tested by the significance of the treatment group by time interaction effect and treatment group main effect. The analysis will be done using SAS Proc Mixed. Similar analyses will be conducted to examine preliminary effects of an exercise intervention on inflammatory cytokines and sleep quality (Aim 4).

Missing data will be created due to the study design because data will not be collected for enrolled participants with a QIDS-C greater than 16 who will be withdrawn from the study to receive treatment for MDD. However, this missing data will not be a source of bias because the proposed mixed-effects models are not biased by data that are missing at random. Data are missing at random if the probability of the data being missing is determined by variables measured in the study. Because the criterion for removal from the study is the observed value of the QIDS-C, we can conclude that missing observations are missing at random and will not bias the mixed-effects analysis.

As a secondary analysis, Kaplan-Meier survival curves stratified by treatment group will be computed for time to initiation of depression treatment. The groups will be compared by log-rank test. A Cox Proportional Hazards analysis will also be done to allow for a covariate-adjusted analysis.

The sample size was based on an analysis conducted to determine the sample size needed to detect an adherence rate of 70% with a Confidence Interval (CI) of ± 12.5 with a probability of 0.80 (similar to using a power of 0.80 in a power analysis). We assumed a standard deviation of 40 as this was greater than the standard deviation for adherence in the TREAD trial (SD = 35), and therefore a more conservative estimate. The table
Assessments is critical to the pilot study to accurately assess the feasibility in collecting this data.

Analyses of proposed mediators of IFN-α will be proposed in a subsequent R01 application to conduct a large RCT the efficacy of an exercise intervention to prevent the development of depression in patients receiving IFN-α treatment. This design includes two intervention arms: 1) a dosed exercise intervention and 2) a health education control group. The rationale for the selection of these two treatment arms was based on previous research, current clinical practices and recommendations of experts in clinical trial design.

In making design decisions, we considered the aims of the proposed study and the stage of the research question. The proposed intervention is novel in that exercise interventions have not been used previously in selective prevention trials of depression. Based on recommendations of Leon et al., the proposed pilot study reflects the design of a subsequent large RCT aimed to determine the efficacy of an exercise intervention to prevent the development of depression in patients receiving IFN-α treatment. This design includes two intervention arms: 1) a dosed exercise intervention and 2) a health education control group. The rationale for the selection of these two treatment arms was based on previous research, current clinical practices and recommendations of experts in clinical trial design.

Exercise dose and intensity. The 12 KKW dose of exercise was selected because it is comparable to exercise doses found to be efficacious in reducing depressive symptoms in patients with MDD. Furthermore, this dose of exercise is consistent with current public health recommendations for physical activity. Similarly, the selected intensity of exercise, 70-85% of maximal HR, has been used in trials demonstrating reduction of depressive symptoms in patients with MDD.

Intervention duration. The duration of the intervention and assessment of primary endpoint was chosen to match the typical duration of IFN-α treatment. We considered an intervention that preceded the initiation of the IFN-α treatment based on data suggesting that baseline levels of depression, sleep and inflammation are related to the development of depression during IFN-α treatment. Our study begins the exercise program 2 weeks prior to initiation of IFN-α treatment. This 2 week timeframe matches the typical clinical course of time between the decision to treat with IFN-α and the initiation of IFN-α treatment. We also considered ending the exercise intervention after 4 months since the development of depression in patients undergoing IFN-α treatment typically occurs within the first 4 months of treatment. However, if our proposed mechanistic model is correct, discontinuation of exercise during IFN-α treatment may result in subsequent development of depression in some patients. We do recognize that exercise “pre-treatment” or shorter intervention durations may be efficacious in reducing IFN-α-induced depression and will consider examining these possibilities in future trials.

Selection of control group. The strengths and weakness of using a HE control group were carefully considered prior to selection. The primary benefit of the HE control group is that it ensures comparable interpersonal contact across the two interventions. As a result, a significant effect observed in the exercise condition cannot be attributed to differences in attention or participation outcome expectations. A potential concern with an attentional control group is a threat to internal validity due to lack of equipoise in treatment fidelity procedures and interventionist allegiance. To reduce these concerns, the HE intervention will be manualized (based on the HE intervention used in STRIDE) and intervention fidelity procedures will be the same across the two interventions. Finally, the study will be described to staff and participants as a comparison of two health-related interventions to eliminate potential expectancy bias.

We also considered a study design to with a comparison group receiving SSRIs. However, because this is a novel intervention we felt it was first necessary to design a trial that would result in the ability to identify the largest possible treatment effect and reduce the likelihood of a Type II error. If our future trial is successful in demonstrating this effect, a future trial comparing exercise to antidepressant medications would be appropriate.

Assessments. The assessments conducted in the current pilot study also match the assessments that will be proposed in a subsequent R01 application to conduct a large RCT the efficacy of an exercise intervention to prevent the development of depression in patients receiving IFN-α treatment. Assessments will be completed by blinded raters to reduce the potential for bias. The subsequent RCT will allow for additional analyses of proposed mediators of IFN-α-induced depression (sleep and inflammation). While the sample size of the pilot study does not allow for a properly powered analysis of these mediators, the inclusion of these assessments is critical to the pilot study to accurately assess the feasibility in collecting this data.

### Design Rationale and Alternative Strategies

In making design decisions, we considered the aims of the proposed study and the stage of the research question. The proposed intervention is novel in that exercise interventions have not been used previously in selective prevention trials of depression. Based on recommendations of Leon et al., the proposed pilot study reflects the design of a subsequent large RCT aimed to determine the efficacy of an exercise intervention to prevent the development of depression in patients receiving IFN-α treatment. This design includes two intervention arms: 1) a dosed exercise intervention and 2) a health education control group. The rationale for the selection of these two treatment arms was based on previous research, current clinical practices and recommendations of experts in clinical trial design.

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<thead>
<tr>
<th>Assumed Standard Deviation</th>
<th>95% CI Width: 70% ± 10</th>
<th>95% CI Width: 70% ± 12.5</th>
<th>95% CI Width: 70% ± 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>44</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>35 (TREAD)</td>
<td>57</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>40</td>
<td>73</td>
<td>49</td>
<td>36</td>
</tr>
</tbody>
</table>

The subsequent RCT will allow for additional analyses of proposed mediators of IFN-α-induced depression (sleep and inflammation). While the sample size of the pilot study does not allow for a properly powered analysis of these mediators, the inclusion of these assessments is critical to the pilot study to accurately assess the feasibility in collecting this data.
Potential Problems
One of the most common potential problems in exercise interventions is assuring adherence to the exercise prescription. We will implement several strategies to help ensure adequate exercise adherence. First, the design of the exercise intervention includes flexibility allowing the participants to schedule sessions around other obligations. Furthermore, while the prescribed dose is intended to be completed in 3 sessions, additional sessions (up to two) may be completed to allow for additionally flexibility in completing the prescribed exercise dose. For the majority of the study, participants will be asked to exercise within a heart rate range of 70-85% of maxHR. This will ensure that participants are exercising at a consistent intensity, but this range will allow for some flexibility in the range to allow participants to exercise at a level that is most comfortable for them. We will also gradually increase the dose and intensity of the exercise over the first 3 weeks of the intervention to allow participants to become comfortable with the exercise program. Additionally, we chose to supervise all exercise sessions to ensure fidelity to the exercise prescription. The DREW study also used supervised sessions and had excellent adherence to the exercise prescription, with 92% of participants completing the 6 month evaluation and these individuals achieved 97% of their target 6 month caloric expenditure in exercise sessions. Finally, a behavioral adherence plan that has been used by Dr. Trivedi in previous exercise trials will be implemented to help retain participants in the interventions and optimize participant adherence. This multi-component behavioral adherence plan incorporates empirically validated behavioral strategies to reinforce participation in the interventions and reduce salient participant- and disease-related barriers to intervention adoption and maintenance. These strategies include: 1) multidisciplinary psychoeducation about adherence; 2) the use of behavioral and monetary reinforcers for attendance/adherence to the intervention; 2) written reference materials; 3) skills training (e.g., instruction in appropriate exercise form, intensity); 4) weekly exercise prescription; 5) self-monitoring of adherence and performance (e.g., heart rate, caloric expenditure); 6) adherence feedback from exercise facilitators; and 7) weekly intervention planning (individually-tailored plan).

Every research study has potential risks to the participants. Several strategies will be implemented to maximize participant safety. All participants will undergo a physical exam and maximal exercise test to be cleared to engage in the exercise intervention. Additionally, participants in the EX condition will have their heart rate and blood pressure monitored prior to, during and after each exercise session. Study staff supervising exercise sessions will be CPR certified and trained to use the available automatic defibrillator. Warm-ups prior to exercise and cool-downs/stretching following exercise will be implemented to reduce the risk of injury associated with exercise. These same procedures have been used successfully in the STRIDE trial. Finally, development of MDD will be monitored in all participants using the QIDS-C. Participants scoring ≥16 (indicating severe depression) will be referred to a psychiatrist for evaluation. Additionally, participants scoring between 11-15 (indicating moderate depression) will be assessed two weeks later. Two consecutive scores of ≥11 will result in referral. The QIDS-C will also be used to monitor suicidality. Any participant scoring ≥2 on item 12 of the QIDS-C will meet with a clinician prior to the participant leaving the clinic.