1. STUDY PROTOCOL: Healing Hearts, Mending Minds in Older Persons with HIV
Short Title: FiT BRAiN

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2. Abstract

By 2015, 50% of persons living with HIV (PLWH) in the United States will be 50 years of age or older. In addition, modifiable risk factors (e.g., obesity, hypertension, dyslipidemia, physical inactivity and other unhealthy lifestyle habits) are more pronounced among PLWH due to HIV disease, antiretroviral therapy (ART), and prior or current risky lifestyles. These factors notably increase the risk for adverse cardiovascular events, but may also promote more rapid decline in cognitive function at significantly younger ages than non-HIV infected persons. Consequently, PLWH age 50 and over represent a highly vulnerable group who are likely to shoulder a disproportionately higher disease burden with multimorbidities. Immune activation is an underlying mechanism shared by the aging process, HIV, and ART treatment that hastens immune senescence and induces a chronic inflammatory state that is associated with greater risk for cardiovascular disease (CVD) and cognitive impairment (CI). Flow Mediated Dilation (FMD) and Pulse Wave Velocity (PWV) for example, markers of endothelial vascular function, have been consistently associated with T cell activation and other inflammatory markers associated with cognitive impairment in persons with and without HIV; FMD and PWV changes however, occur up to 20 years younger and at a more accelerated pace in PLWH. Strategies that reduce CVD and CI risk factors and mitigate the chronic inflammatory state associated with aging and HIV is essential for greater longevity and improved quality of life in this population. Aerobic exercise lowers CVD risk indicators, including inflammatory biomarkers in older adults, and is established to improve physical, psychological, and cognitive function with aging, but has limited testing in PLWH. Animal research has provided the most robust evidence that aerobic exercise stimulates neuronal growth and synaptodendritic complexities involved in learning and memory with increasing levels of brain derived neurotrophic factor (BDNF) possibly playing a crucial role in this process. Regular aerobic exercise performed 5 times per week for 150 minutes has also been shown to improve aspects of neurocognitive function in community-dwelling older adults. Only one exercise study however, has examined the effect of exercise on cognition in PLWH and was limited by a self-reported, unreliable indicator of cognitive status. No studies have reported whether exercise improves cognition in this population using objective assessments or examined the potential mechanisms involved. Our home-based aerobic exercise intervention, the '*Let's Move Program*' has been tested and is effective for lowering CVD risk in previous trials of older caregivers and adults with advanced CVD. The proposed efficacy trial will accrue 200 participants, allowing for 20% attrition over the course of the study, resulting in a final sample of 160 to be randomized to one of two groups (Lets Move (n=132) and Lets Flex (n=68). Participants will be ≥ 50 years of age, sedentary, demonstrate objectively measured CI, and stable on antiretroviral medications for at least 6 months. Motivational Interviewing (MI) will be used to promote exercise self-efficacy and optimize adherence to the intervention and promote flexibility and stretching in the attention control arm.

3. Introduction and Background

By 2015 more than half of HIV-infected individuals in the U.S. will be older than 50 years of age.[1-3] Two phenomena contribute to the "graying" of the HIV epidemic. The overwhelming success of antiretroviral therapy (ART) has improved life expectancy and dramatically changed the trajectory of HIV; it is now a complex chronic condition, often accompanied by multiple comorbidities such as cardiovascular disease (CVD) and cognitive impairment (CI). Second, increasing numbers of middle-aged and older adults are becoming infected with HIV. Individuals age 50 years and older are also among the newest populations at risk of HIV infection, representing 10.8% (5,400 cases) of new infections in the U.S. per year.[4] Clinicians, patients, and society are currently ill-prepared to deal with the biomedical complexities and unique medical and psychosocial challenges associated with the growing aging HIV population.[3]

Cognitive impairment (CI) is one of the most common comorbidities among older persons living with HIV (OPLWH). In the era of ART, HIV Associated Neurocognitive Disorders (HAND) occur in 40-50% of PLWH across all ages, and are primarily characterized by mild to moderate deficits in executive function and episodic memory.[5] OPLWH are at greater risk for HAND than their younger counterparts with prevalence rates of HAND *nearly twice* that seen in younger HIV infected persons.[6, 7] A greater prevalence of CNS affecting comorbid conditions among older persons (both with and without HIV)[8] and more rapidly advancing HIV disease[9] increase the likelihood for HAND. Of note, a number of brain changes including less synaptodendritic complexity,[10] volumetric loss,[11] and changes in blood flow to and within the brain[12] have been postulated to further increase cognitive decline. Cognitive deficits are linked to problems in key areas needed for independent living including medication adherence,[13] financial management,[14] and driving,[15, 16] all areas in which older adults living with HIV experience higher rates of disability. With the growing population of OPLWH [17] efforts to improve the cognitive functioning and capacity for independent living among this group are critical.

In addition, OPLWH are at significantly higher risk for CVD including coronary artery disease, myocardial infarction, peripheral artery disease and chronic heart failure compared to younger PLWH[17-20] and experience the onset of these conditions at significantly younger ages than the HIV-negative population.[1] Physiological and metabolic abnormalities in HIV appear to accelerate vascular stiffening, contributing to increased risk for CVD and cognitive decline.[21] Importantly, in the general population, cerebrovascular disease is the second most common cause of acquired cognitive impairment.[22] Mechanisms associated with vascular cognitive impairment vary with its severity but can include risks such as reduced cerebral perfusion,[23] white matter lesions, brain infarcts, and hemorrhages.[24] Moreover, the blood-brain-barrier and neurovasculature are disrupted and malfunction in patients with vascular cognitive impairment. This can result in, among other things, an inflammatory response leading to problematic cerebral autoregulation.

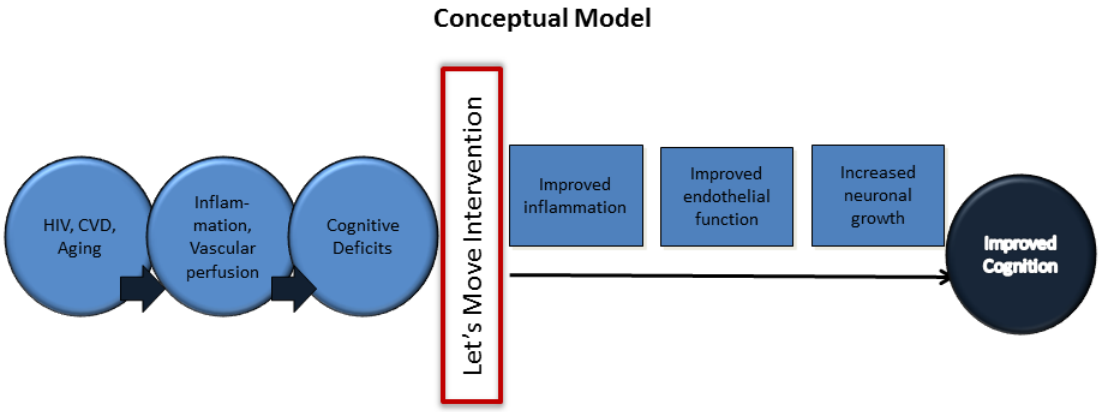
Cerebral inflammatory processes are also implicated in the development of HAND. Although the precise mechanisms responsible for the development of HAND are currently unknown, it is suspected that replication of HIV in the central nervous system (CNS), particularly deep in the brain structures of the basal ganglia and adjacent subcortical white matter,[25, 26] is a likely contributor. Because HIV does not directly infect significant numbers of neurons, neuronal damage including decreased neuronal counts, abnormal and decreased dendritic arborization and neuronal apoptosis is believed to be secondary to the production of neurotoxic factors by activated macrophages and microglia.[27] These neurotoxic factors include inflammatory cytokines, markers, neuronal growth factor, oxidative stress, thrombotic tendency, and endothelial vascular function.[27-29] Older individuals may be especially sensitive to this inflammatory cascade, given studies in laboratory animals and humans demonstrating increased microglial activation even in the absence of infection.[30] This so-called microglial priming as a function of aging may further contribute to an exaggerated inflammatory response to HIV infection in older individuals leading to increased likelihood of HAND.[30, 31]

Therefore, HIV infection, CVD, and biological aging are each associated with inflammatory responses potentially leading to cognitive decline. Given the growing numbers of OPLWH and the potential debilitating effects CI has on one's ability to function independently, identification of interventions that can slow or prevent risk for cognitive decline are essential. A dramatic increase in the prevalence of CVD is also anticipated in OPLWH in the next several decades (≥45 years/<45 years 16.4 vs. 4.2%), indicating the essential need for developing effective strategies to reduce CVD risk and inflammation among OPLWH.[32]

Exercise. Mounting evidence suggests that moderate physical activity can be used as a treatment to improve and/or prevent cognitive decline. The majority of this evidence comes from animal models and older adults.[33-35] In non-HIV infected older adults, observational and epidemiological reports have shown a significant relationship between level of physical activity and cognitive function implying that exercise may have a neuroprotective effect on later life cognition. For example, Yafee[36] found cognitive performance improved with increasing physical activity levels. Fitness training in meta-analytic studies show robust, selective gains for cognition, with executive-control processes showing greatest benefit (moderate effect size of 0.48). Cognitive and physical function as well as positive behavior among older adults with dementia or other forms of CI also show significant improvements (e.g., effect size of 0.62 across all outcomes in meta-analysis) with physical exercise. [37] Collectively, intervention studies conducted in older adults favor a causal relationship between aerobic exercise and improved cognition, more efficient brain functioning and less brain volume loss. Evidence from other populations, including those with disabilities and chronic illness, (e.g. renal failure, Parkinson's Disease, multiple sclerosis, stroke, Alzheimer's Disease) suggests that exercise improves cognition via several biological processes: its impact on increased cerebral blood flow and oxygen delivery; its influence on BDNF (thought to enhance neurogenesis); and its effect on certain neurotransmitters.[33, 34, 38-45] Our preliminary work indicated that participants with better physical function had less difficulty with memory and concentration than those with poorer physical function.[46] Exercise is reported to improve cerebral oxygenation following moderate intensity aerobic exercise, but few studies have examined this directly in clinical populations or the impact on cognitive functioning in well-designed studies.[43] As stated above, the effect of exercise is much greater on selected cognitive processes, especially executive function suggesting it may be amenable to intervention.[38, 39, 44] This finding has important implications for OPLWH whose executive functioning is particularly affected by the underlying pathological changes associated with HIV.[47] Only one study has examined the effect of exercise on cognitive functioning in HIV infected individuals. Filipas et al.,[48] reported a significant 14 point improvement in self-reported cognitive function using the Medical Outcomes Study HIV Survey in HIV infected men a following a 6 month exercise training program. However, self-report cognitive functioning measures are highly influenced by fluctuations in mood and are often invalid when objective neuropsychological testing is conducted.[49] The effects of aerobic exercise on neurocognitive function in OPLWH using standard, objective neuropsychological testing has not been reported to our knowledge. Mechanisms by which exercise may improve cognitive functioning among OPLWH include improved physical function, anti-inflammatory responses, and blood flow and oxygenation as well as reduced CVD symptoms.[50-52] Increasing age and BMI are associated with poorer cardiorespiratory fitness in HIV-infected populations, which in turn increases risk for CVD and adverse cardiac events. Reductions in CRF have primarily been attributed to sedentary behavior and lifestyle habits. For example, PLWH often exhibit maximal oxygen consumption (VO_2) that is 24% - 44% below their age-predicted normal values for cardiorespiratory fitness and up to 50% fail to meet daily recommended physical activity guidelines.[53-55] Short duration studies have shown significant increases in cardiorespiratory fitness with moderate or high intensity exercise training in as little as 6 weeks, in addition to a dose response to aerobic exercise when performed at least 2-3 times per week.[50-52] Other beneficial physiological and anthropometric adaptations include increased serum HDL-C, decreased triglycerides, reduced abdominal circumference and total cholesterol, but the metabolic outcomes have been inconsistent and long-term evaluation of exercise has not been reported.[52, 56-60] Exercise has also been associated with improved inflammatory, vascular and endothelial outcomes in non HIV infected persons, but has not been well studied in PLWH,[52, 61, 62] and no studies have specifically evaluated these variables in OPLWH. In one study, endurance and strength training decreased plasma IL-18, whereas aerobic exercise alone also decreased other inflammatory markers (TNF-alpha, IL-6, and hs-CRP) in 39 HIV infected men whose mean age was 53± 8 years.[60] Psychological well-being and quality of life (QoL) in PLWH have also reportedly improved following exercise interventions, similar to that reported in non HIV infected individuals. Evidence shows that exercise can reduce depression and fatigue which are common symptoms that considerably lowers QoL in PLWH.[52, 61, 62] For instance, up to 50% of PLWH experience depressive symptoms. Whether these symptoms persist, worsen or may be improved in OPLWH is less clear.[63, 64]

Home-Based Exercise in HIV. Exercise interventions that require regular attendance at a site based facility are not ideal for populations with low socioeconomic status or such as OPLWH, due to difficulties associated with transportation, access, and cost.[65] Low adherence to prescribed exercise and high attrition rates have been documented in site based programs for both HIV infected and uninfected individuals.[52, 56] Despite the convenience and cost effective approach, few home-based exercise studies have been reported in PLWH.[66-68] Dolan[67] used a 16 week home-based program of aerobic exercise and resistance exercise in HIV-infected women and reported significant improvements in cardiorespiratory fitness, strength and waist circumference among the exercisers compared to controls. Further, the exercise group had no adverse events, few drop-outs and a high adherence rate of 95%. This home-based approach however, provided a stationary bicycle and other equipment at a cost of approximately $400 per participant. In addition, each participant was visited 3 times per week for 16 weeks by a physical therapist, none of which are feasible in most practice settings. Although this expensive and labor intensive study had positive outcomes, it is not known if the participants continued to exercise after the study concluded and the equipment was removed. As more PLWH are advised to exercise, clinically feasible, cost effective and sustainable programs will become increasingly important to manage CVD risk reduction.[52] We have used aerobic home-based programs successfully in several studies of older, ethnically diverse adults.[46, 69-71] The proposed project will expand our prior experience with aerobic exercise protocols to OPLWH measuring similar biomarkers and outcomes. A novel aspect of the aerobic exercise intervention will be to employ group delivered motivational interviewing that we previously tested and was well received.[72] This study will also allow us to test methods and process evaluation data with the goal of disseminating an effective approach to increasing exercise for CVD risk reduction and potentially attenuating CI in OPLWH.

Conceptual Framework. A visual depiction of how the proposed Let's Move aerobic exercise intervention may improve cognitive functioning is presented in the figure. HIV-infection, CVD, and the aging process increase inflammatory responses and reduce vascular brain perfusion (either directly or through effects of medications).[73-80] We propose that the Let's Move intervention will improve cognitive function through the ability of aerobic exercise to reduce inflammatory markers neuronal growth factor, oxidative stress, thrombotic tendency, and endothelial vascular function .[52, 61, 62, 81] Aerobic exercise is proposed as a strategy to enhance neurocognitive function by reducing CVD risk factors and the associated inflammation that contributes to atherosclerosis and poorer endothelial vascular function. Aerobic exercise has been shown to improve cerebral oxygenation and perfusion in other chronic illness populations and in some cases improved cognition.[35, 82] A novel biomarker BDNF is also proposed to enhance neurogenesis and in turn, cognitive functioning.[33, 41, 45] Regardless of whether the relation is due to shared risk factors or to direct and indirect influences of CVD on brain pathology, aerobic exercise designed to reduce CVD risk factors are plausible strategies to prevent, slow, or even reverse cognitive decline in vulnerable aging PLWH with CVD risk factors and CI.



The *Let's Move* program also integrates Social Cognitive Theory (SCT)[83] and Motivational Interviewing (MI)[84, 85] to facilitate adherence to the intervention. SCT posits that change in behavior and maintenance of that behavior result from expectations about one's ability to perform a certain behavior (self-efficacy or efficacy expectation) and the expectation regarding the outcome resulting from that behavior (outcome expectations). SCT has been commonly used to examine exercise behaviors across a number of chronic illnesses, including

HIV.[48, 86] Self-efficacy expectations and outcome expectations (less frequently examined) are associated with increased exercise adherence in these studies. Self-efficacy is developed through past experiences from 4 primary sources: 1) performance accomplishments, 2) verbal persuasion from others, 3) social modeling or vicarious experiences (exercise video), and 4) physiological and emotional states or cues.[83, 87] The *Let's Move* program includes information about the importance of exercise, emphasizing individualized graded exercise, incorporating self-monitoring techniques, setting achievable goals, providing feedback about exercise and reinforcing progress, and use of cognitive behavioral strategies for developing and providing feedback on the use of positive coping strategies.[87]
Motivational interviewing (MI) is a client centered directive counseling method that helps clients resolve ambivalence and resistance toward and build motivation for behavior change.[84, 85] MI counseling has been successful in changing many health behaviors including HIV medication adherence.[67] MI emphasizes collaborative partnerships, supports autonomy in decision-making, and elicits information about one's motivations.[84, 85] A trained individual will employ MI strategies in groups and during phone contacts to empower participants to work through ambivalence about exercise, overcome barriers to exercise and build self-confidence (self-efficacy) for exercise and reinforce regular exercise.[72, 87]

4. **Objectives**

Our home-based aerobic exercise intervention, the '*Let's Move Program*' has been tested and is effective for lowering CVD risk in previous trials of older caregivers and adults with advanced CVD.[70-73] The proposed efficacy trial, Fit BRAiN will recruit 200 PLWH and randomize them (2:1) to either the *Let's Move intervention* (n=132) or an attention control condition*, Let's Flex (*n=68), and follow them for an additional 3 assessments/time points (at 13-15 weeks post baseline, 28-30 weeks post baseline and again at 56-58 weeks post baseline). Participants will be ≥ 50 years of age, sedentary, demonstrate objectively measured CI, and stable on antiretroviral medications for at least 6 months. Motivational Interviewing (MI)[74-75] will be used to promote exercise self-efficacy[76-77] and optimize adherence[78] to the intervention and flexibility and stretching to the attention control arm. The following are our aims:

AIM 1: To test, in a RCT, the efficacy of the *Let's Move Program* to improve cognitive functioning in this sample.
H0 1: Participants in the *Let's Move* intervention will have significantly higher scores than participants in the Let's Flex attention control group on measures of executive skill, episodic memory, and information processing speed at 3 assessments/time points (averaging a total of 56-58 weeks) post-baseline.

AIM 2: To test, in a RCT, the impact of the *Let's Move Program* on inflammatory markers, endothelial vascular function, and neuronal growth factor (BDNF) in this sample.
H0 2: Participants in the *Let's Move* intervention will demonstrate improved *inflammatory markers, neuronal growth factor, oxidative stress, thrombotic tendency, and endothelial vascular function* compared to the Let's Flex attention control group at 3 assessments/time points (averaging a total of 56-58 weeks) post-baseline.

Secondary Aim: To explore the potential mediation effects of inflammatory biomarkers, endothelial vascular function, and neuronal growth factor on the relationship between the *Let's Move Program* and the cognitive skills measured in Aim 1.

5. Study Design and Methods

All procedures performed in this study are for research purposes only.

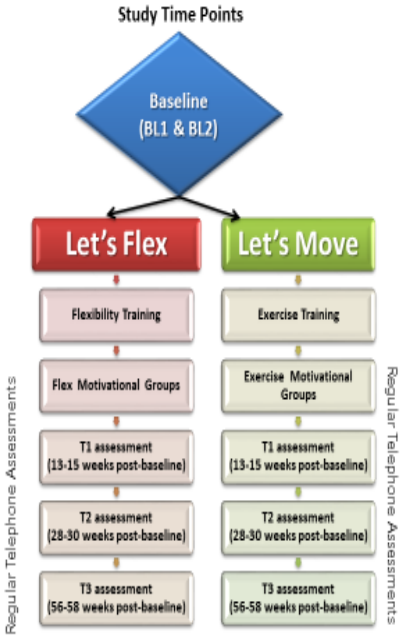
FiT BRAIN Study Design. We propose a 4-year, two-arm 2:1 RCT design to test the longitudinal effects of the Lets Move Program compared to an attention control group, the Lets Flex Program. We will accrue 160 participants, allowing for **20% attrition** over the course of the study, resulting in a final sample of **128 to be**

randomized to one of the following 2 groups: Lets Flex (n=107) and Lets Move (n=53). Outcomes of interest include markers of CVD risk and cognitive functioning. Measures will be taken at **Baseline, T1 (13-15 weeks post-baseline), T2 (28-30 weeks post-baseline), and T3 (56-58 weeks post-baseline)**. The ultimate goal of this study is lifestyle modification rather than a one-time intervention. The intervention is thus approached using behavioral change activation and maintenance strategies (e.g., motivational methods, long-term monitoring, and booster sessions).

Phase 1: Pre-enrollment preparation (0 - 9 months): Prior to initiating data collection, all recruitment, intervention materials, forms, and procedures will be refined and protocol manuals established. The recruitment and intervention materials will be reviewed by the Community Advisory Board (CAB) at the Ponce Infectious Diseases clinic for relevance, readability, cultural appropriateness, accuracy, and acceptability. Investigators will periodically retrain and assess adherence to intervention protocols by randomly selecting sessions to attend or phone calls to record and evaluate according to protocol quality indicators.

Phase 2 (9-48 months) Implementation of the RCT. We will conduct a 2 arm (Let's Move treatment condition vs. Let's Flex attention control condition) RCT among **160** sedentary OPLWH ages 40 and over who are stable on antiretroviral medications for at least 6 months and have cognitive impairment (see inclusion criteria below). Variables of interest will be measured at baseline, T1 (13-15 weeks post-baseline), T2 (28-30 weeks post-baseline), and T3 (56-58 weeks post-baseline)**.**
Study sites: Three Atlanta area HIV/AIDS primary care clinics will be recruitment sites: The Ponce de Leon Center of the Grady Health System, the Emory Hospital Infectious Diseases Clinic, and AbsoluteCARE, Inc. Patients served represent a wide range of SES and demographic groups across all clinics (> 50% of patients are African American).[91] Combined, the clinics serve a total of nearly 8900 patients of whom **about 2500 are aged 50 and over**. This provides a substantial pool of potential participants.

Assessments Time Points. At baseline (BL), all study measures listed below (see tables 4-7) will be administered. These same measures will also be completed at T1 (13-15 weeks post-baseline), T2 (28-30 weeks post-baseline), and T3 (56-58 weeks post-baseline). The total time to complete each study visit (except the booster) is expected to be approximately 6-8 hours. The PIs' earlier studies with similar populations included study visits lasting a similar length of time. With mandatory, scheduled breaks, snacks, and lunch provided (post-blood collection), participants are able to complete each study visit over two days.



Study arms. Randomization procedures.
Randomization will occur after completion of the first baseline assessment; after the study cardiologist reviews the participant EKGs from a treadmill stress test and prior to the second baseline assessment visit. Randomization of participants will be stratified by site to ensure a similar distribution in subjects' demographics and estimated premorbid IQ between the treatment groups. At each of the three recruiting sites, participants will be randomized to the *Let's Move* intervention arm or to the *Let's Flex* attention control arm in a 2:1 ratio. During the first and second baseline assessment visits, participant will be provided a schedule of events, copies of informed consent and project office phone numbers, and instructions on how to prepare for the first evaluation which will include fasting blood work and the exercise treadmill test.

Intervention Arm: ***Let's Move Program.***

- **Treadmill Test** - Dose-specific exercise will be based on maximum heart rate (HR) obtained during a symptom limited, modified Balke or Bruce treadmill test[95, 96] conducted by an exercise physiologist and supervising clinician at the Clinical Research Network (CRN). Target heart rate (THR) using the 60% to 70% of maximum HR achieved on the cardiopulmonary exercise test will be used to monitor the intensity and training response for aerobic exercise.
- **Home Exercise Training –** After the study cardiologist clears a participant to continue in the study after reviewing their EKG from a treadmill stress test, a second participant visit within 12-weeks post treadmill test will be conducted at the research office to develop an individualized "exercise prescription" to be done at the participant's home to ensure that participants achieve adequate training stimulus. Each participant will be provided with an individualized target heart rate zone based on the treadmill testing results.[97] Under the supervision of a research staff, participants will be instructed to begin the walking sessions at 60% of target heart rate and increase to 70% by week 5 as shown in Table 3. In our pilot work, a progressive moderate intensity level exercise program yielded positive outcomes with no adverse events, was appealing to participants and adherence rates were 80% or higher.

Table 3. Aerobic exercise progression prescription for Let's Move intervention

	Weeks 1-2	**Weeks 3-4**	**Weeks 5-8**	**Weeks 9-12**	**Weeks 13-58 (maintenance)**
Intensity	60%	60%	70%	70%	70%
Duration	30 minutes	45 minutes	45 minutes	60 minutes	60 minutes
Frequency	5 times per week	5 times per week	5 times per week	5 times per week	5 times per week

Participants who are unable or unwilling to leave the home will have a DVD/video provided from the National Institute of Aging (NIA) and the American College of Sports Medicine (ACSM) to guide their exercise sessions. The NIA/ASCM exercise guides and DVD/video will be used to structure this activity. The 48-minute video, "*Exercise & Physical Activity: Your Everyday Guide from the National Institute on Aging"* that emphasizes measures to increase aerobic activity while in the home such as walking in place while watching television and other aerobic exercises that can be performed at moderate intensity level. A DVD player will be provided for the duration of the intervention if needed.

- **Group Motivational Interviewing (MI) (4 sessions)** -MI groups will occur after the second visit and within 4 weeks. Each intervention group and attention control arm at each clinic will attend 4 separate group intervention sessions for 1.5 hours for 4 consecutive weeks. *Participants will have initiated their individualized home-based program by the first group.* Groups will consist of 4-8 members and content will focus on the rationale for aerobic exercise for the intervention group and stretching for the attention control arm. The content of the intervention group will focus on reducing blood pressure, lipids, CVD risk, enhancing muscle oxidation and function, reducing risk for physical function decline, barriers to exercise, finding time for exercise, how to set short and long term exercise goals, and use of self-monitoring (pedometers, Fitbits, polar heart watches, perceived exertion) to improve exercise engagement in the intervention group. In the attention control arm the focus will be on flexibility and stretching. MI strategies will be employed in the group discussions to foster commitment and confidence for behavior change and to help participants explore and resolve ambivalence about incorporating exercise or stretching. It is expected that the group sessions will promote effective problem solving as participants discuss challenges and responses to these challenges for integrating healthier lifestyle behaviors. During the group sessions, the research staff member(s) will review step calendars, download polar HR monitors for adherence and intensity level, review pedometer and/or Fitbit step data for the prior week in the intervention group and the attention control arm as well as monitor exercise intensity and duration based on these data in the intervention group. Once the 70% intensity level is achieved, the duration of exercise will be progressed at 5-10 minute intervals to reach a maximum of 60 minutes, 5 times per week. Weight and healthy messages using MI to set goals for exercise and healthy lifestyles will also be included for the intervention group and goals for flexing/stretching for the attention control arm. Attendance at all sessions will be

emphasized; however, if absent from a session, participants will receive phone calls and encouraged to attend a make-up session.

- **T1 assessments** - Participants will continue their at-home individualized exercise/stretching program and complete assessments included in tables 4-7 below at T1 (13-15 weeks post-baseline). Pedometers, Fitbits and/or HR monitors will be downloaded (via Fitbit.com or Fitabase), step calendars reviewed, at the T1 visit to monitor adherence and adjust exercise intensity or duration if needed with the intervention group. Participants in this group will be counseled on exercise prescription based on the data retrieved from the Fitbit/Polar HR watch and exercise logs. For example, if they are exercising at 70% intensity, the duration will be progressed. **Weekly telephone monitoring** will occur from end of MI groups up to the T1 assessment using the FITT model (frequency, intensity, time and type of activity) to monitor progress and facilitate working through barriers related to exercise. An interventionist log will be used to record specific goals, barriers and problem solving strategies discussed with the participant. In addition these theoretical and intervention process measures, cognitive outcomes, biological, physical and psychological measures will also be done at T1 assessment visit.
- **T2 assessment and T3 final assessment** – Similar to T1 assessment, exercise/stretching programs are to be maintained after the T1 assessment through completion of the study at the final T3 assessment. At T2 and T3 assessments, the same measures listed in tables 4-7 will be completed. Also, at **T2 (28-30 weeks post-baseline)**, MI techniques as well as measures listed in table 7 will be completed. The research staff will contact the participant and will re-evaluate strategies as needed to maintain the exercise/stretching program. Fitbits, HR polar monitors, pedometers, and step logs will be downloaded and reviewed. **Telephone monitoring will take place bi-weekly** from T1 to T2 and **monthly** from T2 to T3 assessment, the end of study enrollment.

Process Evaluation: Documentation of the delivery of the intervention will be provided through research assessment visits and telephone calls, plus participant evaluation of the group sessions. The Fitbits, polar HR monitor data, step logs, and pedometer data will be monitored during the group sessions and telephone calls and collected at each scheduled study visit. Research staff performing the intervention will use a quality indicator form to record their delivery of specific aspects of the intervention each session, difficulties encountered, and questions or issues raised by participants. These data will be entered into the database in the form of field notes which will be text-analyzed for themes. Participants will also be asked to evaluate the benefits of the sessions as well as make suggestions for improvement.

Attention Control (AC) Arm: *Let's Flex Program*. As delineated in the figure above, all study assessments will also be completed by the Let's Flex attention control condition participants. Content of the sessions and all contact will be on flexibility and stretching and will provide control for the possible confounding variable of receiving an exercise program and is also expected to reduce attrition and patient dissatisfaction and to better ensure concealment of group allocation. These time-equivalent flexibility/stretching movements have been previously piloted and were well received, but were not strong enough to influence cardiovascular or biomarker outcomes. For ethical and cardiovascular health reasons, the AC group will be advised to exercise, but will not be provided with education on exercise, nor receive an exercise prescription. The AC group will only be provided with stretching information. Let's Flex participants will document adherence to the flexibility protocol on a Let's Flex log that will be reviewed during groups/visits. Assessments at each time point indicated in tables 4-7 will also be completed with the AC group identical to the intervention group.

Drug and Alcohol Screening. To maintain accurate results and scores for tests in tables 4-6, research participants may be asked to take a drug and alcohol screening test. Drug screening will be administered through iCup urine drug test kits (or similar testing method). Drug screening will be conducted to test for COC (cocaine), THC (marijuana), OPI (opiates), AMP (amphetamine), and mAMP (*meth*-amphetamine). No technical or certified training required to administer iCup drug test kits. Drug test kits will be administered according to the manufacturers' recommendations and instructions. Results for the drug screening will be available within 5 minutes and positive results for any of these drugs will lead the research staff to reschedule participants to take the tests in tables 4-6 another day. Similarly an alcohol screening will be administered via a

breath analyzer (i.e., Akers Bioscience). The breath analyzer will measure blood alcohol concentration (BAC) and the tests will be administered according to the manufactures' recommendations and instructions. BAC results ≥ 0.05 or 0.08 will also lead the research staff to reschedule participants to take the tests in tables 4-6 another day. BAC level of 0.05 begins to show impairment in concentration and coordination and 0.08 is the drunk driving limit and shows definite impairment in coordination and judgment.

Retention plan and incentives. To encourage and monitor retention we will call, text, and/or send appointment reminders to participants and maintain an extensive locator form with several contacts for each participant. This will be updated at each study visit. Alternate contacts will be called when we are unable to locate a participant. All participants will receive an incremental increase in compensation to help retain participation and reduce attrition total of $115 for completing baseline (BL) assessments ($50 for BL1 and $65 for BL2), a total of $40 for T1 ($20 for T1a and $20 for T1b), a total of $60 for T2 ($30 for T1a and $30 for T1b), and a total of $100 for T3 for time and travel for each of the 3 study assessments; snacks and/or meals will be provided during the assessments. All participants will receive an additional $20 for each of 4 motivational interviewing (MI) group sessions for a total of $395 per participant over 56-58 weeks (13-14 months). Some travel will also be compensated (i.e., one-way MARTA cards, parking validation, or travel services).

Study Assessments.

Cognitive Outcome Measures will be used to measure the primary outcome variables at BL, T1, T2 and T3 assessments. Cognitive outcome measures will be measured at the second visit for baseline after the study cardiologist has cleared a participant to continue with the exercise study after reviewing their EKG from a treadmill stress test. These outcome measures have been effectively used to examine neurocognitive functioning and treatment effectiveness in numerous clinical trials and in persons with wide-ranging medical conditions, including those who have HIV/AIDS. Table 4 lists the selected measures for the proposed study, domains assessed, a brief description of each, primary variable(s), and administration time. The outcome measures reflect the areas of executive functioning, episodic memory, and processing speed hypothesized to be affected by the exercise intervention based on findings in the research literature.[100] Four parallel forms are available for the memory measures to reduce potential practice effects associated with repeated presentation of the same to-be-learned stimuli. Dr. Goldstein, the project neuropsychologist, will provide outcome assessment training and continuous monitoring of data collection and quality. The examiner will code the reliability of each test score, any alteration of standard procedure, and the reason.

Table 4. Cognitive Outcome Measures

Measures	Description	Time (min.)
Stroop Color and Word Test	The Stroop Color and Word Test consists of a Word Page with color words printed in black ink, a Color Page with 'Xs' printed in color, and a color-Word Page with words from the first page printed in colors from the second page (the color and the word do not match). The respondent goes down each sheet reading words or naming the ink colors as quickly as possible within a time limit. The test yields three scores based on the number of items completed on each of the three stimulus sheets	
Trail Making Test A & B	The Trail Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It is sensitive to detecting several cognitive impairments such as Alzheimer's disease and dementia	
Letter Fluency	(FAS) The FAS test requires stating out loud as many words that begin with the assigned letter as possible within 60-seconds.	
Category Fluency	(Animals) The Category fluency test requires stating out load the names of as many animals as possible within 60-seconds.	
Hopkins Verbal Learning Test - Revised	This is a list learning task requiring the respondent to recall as many words as possible from a list of 12 words provided orally by the examiner. There is a learning trial, a delayed recall trial, and a recognition trial.	

Brief Visual Memory Test - Revised	This test is a non-verbal equivalent to the HVLT-R and requires that respondents reproduce simple visual images from memory (the images are displayed for 10 seconds then removed). The BVMT-R contains a learning trial, a recall trial, and recognition trial, and a copy trial.	
Grooved Pegboard	This test requires the placing of grooved pegs into a same-shaped hole as quickly as possible, once with the dominant hand and once with the non-dominant hand.	
Finger Tapping Test	This test a fine motor speed requires tapping a lever with the index finger as quickly as possible. Trials with the dominant and non-dominant hand are completed.	
Coding	This test requires writing the corresponding symbol associated with a letter from a key provided. As many responses as possible are completed in the 120 second time limit.	
Digit Span	The digit span test requires repeating an increasing span of digits that are provided verbally by the examiner. The test includes trials of repeating digits in the same order presented by the examiner and in the reverse order of that presented by the examiner.	
Spatial Span	Spatial span requires repeating in both forward and reverse order, the sequential order of blocks presented by the examiner.	
Symbol Span	Working memory, Letter-number sequencing. The subtest assesses visual working memory using novel visual stimuli. A series of abstract symbols on a page are shown briefly. Then the symbols are to be selected from an array of symbols in the same order they were presented on the previous page.	
Instrumental Activities of Daily Living (IADL)	This is a self-report measure assessing the amount of assistance, if any, required to do day-to-day tasks necessary to live independently.	
NIH Toolbox	Computerized cognitive tests developed and distributed by the NIH. Tests include Pattern Comparison Processing Speed Test, Picture Vocabulary Test, Reading Recognition Test, Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, List Sorting Working Memory Test, and Oral Symbol Digit Test	

Blood collection procedures: After overnight fasting, all blood samples will be collected with an intravenous (IV) catheter will be placed into a forearm vein or hand. Blood samples will be collected by a research staff or laboratory assistant trained in blood drawing techniques after 30 minutes of rest between 8-11:30 am (to control for circadian variation) in EDTA or Heparin tubes and immediately placed on ice. Where indicated, blood will be spun at 3,000 rpm for 15 minutes at 4C. Plasma samples will be coded, labeled and will be aliquoted into pre-cooled siliconized polypropylene tubes and stored at -80C until assayed for relevant biomarkers. Processing and analyses of specimens will be performed according to manufacturer ELISA recommendations. Blood collection for the measures in Table 5 will occur at **Baseline, T1, T2 and T3 assessments.** When the study is completed, the blood sample will be destroyed.

Flow mediated Dilation (FMD): A forearm test will be conducted to measure endothelial function at **Baseline, T1, T2, and T3 assessments** after overnight fasting. Participants will have a blood pressure cuff placed around one of their arms. The blood pressure cuff will be inflated and deflated and a trained clinical staff will use an ultrasound device to take measurements of the blood flow in the participants arm.

Table 5. Biological Measures

Measures	**Description**
Inflammatory Biomarkers	
Soluble Cluster of Differentiation 14 (**sCD14**)	Marker of monocyte activation, is associated with neurocognitive impairment and HANDs and higher mortality in PLWH. [19-21, 23, 79-80]
Interleukin 6 (**IL-6**)	IL-6 is a well-established pro-inflammatory cytokine known to contribute to the pathogenesis of insulin resistance that contributes to increased risk of CVD and CI through inflammation and promotion of endothelial vascular dysfunction. IL-6 has also been associated with both depression and fatigue in both medically ill and medically healthy individuals. [2, 29, 103]
Tumor Necrosis Factor alpha (**TNF-alpha**)	TNF-alpha is a potent proinflammatory cytokine a key mediator of neuroinflammation and contributes along with microglia activation to neuronal dysfunction.[109] Elevated levels of TNF-α have been documented in several neurodegenerative disorders including HIV-associated dementia.[110] TNF-α signalizng disrupts hippocampal activity patterns underlying learning and memory.[109]

High sensitivity C-Reactive Protein (**hsCRP**)	A well-established risk factor for cardiovascular and cerebrovascular disease and higher levels are associated with increased mortality in HIV (Boulware 2011)
Soluble urokinase Plasminogen Activator Receptor (**suPAR**)	This inflammatory biomarker is associated with higher risk for CVD in persons with HIV.
Neuronal Growth Factor	
Brain-Derived Neurotrophic Factor (**BDNF**)	In the brain, BDNF is active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking. BDNF itself is important for long-term memory.[33, 34, 39-43, 45]
Oxidative Stress	
Thiobarbituric Acid Reactive Substances (**TBARS**)	Associated with Vascular function and oxidative stress in persons with HIV
Thrombotic Tendency	
D-dimer	Marker of procoagulation, associated with increased risk for CVD and neurocognitive decline in older adults
Vascular Function	
Flow-Mediated Dilatation (**FMD**)	A well validated measure of endothelial function, has been shown to be correlated with sCD14, IL-6 and D-dimer levels in PLWH
Pulse Wave Velocity (**PWV**)	Increased PWV is associated with impaired vascular function and CV.

Several physical and psychological function measures will inform potential covariates or other explanatory variables that may influence study findings. These will be measured at **Baseline, T1, T2 and T3 assessments.** Psychological measures will be administered via Audio-Computer Assisted Survey Instrument (A-CASI) or on-line survey tool (e.g., NIH PROMIS assessment center). If participants report that they are having suicidal thoughts to the BDI-II questions, the study psychiatrist (Andrew Miller, MD) and/or the Principal Investigator(s) will be contacted so that he/they can talk with the participant. If necessary, he/they may require that the participant is admitted to a hospital facility for your suicidal thoughts. Assistance will also be provided to participants to find a counselor if they are feeling depressed.

Table 6. Physical and Psychological Function Measures

Measures	Description
CHAMPS	The 41-item Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire (CHAMPS) *(revised)*[116] which respondents report weekly frequency of participation and weekly duration in a typical week over the last 4 weeks. The CHAMPS instrument has strong psychometric properties and is sensitive to change for various activity levels in older adults and has been used extensively in exercise intervention studies.[117, 118] The CHAMPS has also been validated in culturally diverse groups including African Americans.[119]
$V0_2$ max	V02 max is a measure of cardio-respiratory fitness. A symptom limited Balke treadmill test[95, 96] will be used to determine maximum HR and $V0_2$ max for exercise prescription and to screen for potential cardiac contraindications to exercise according to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines.[96] A certified exercise physiologist will administer the test, and the cardiologist supervising the exercise test will interpret the ECG data. Maximal metabolic equivalents (METs) attained them to read and explain the informed consent. During the test (1 MET = resting metabolic rate, defined as an oxygen uptake of 3.5 mL x kg^{-1} x min^{-1}) will also be calculated. In our previous work, the modified Balke was well tolerated and without adverse events in older adults.
BDI-II	The Beck Depression Inventory-II (BDI-II)[120] is a well validated measure and has been widely used in the HIV population for determining depressive symptoms. We will evaluate both somatic and cognitive subscales to evaluate depressive symptoms. The BDI II will be used to screen and monitor for depressive symptoms and suicide ideation.
PSS	Perceived Stress Scale (PSS)[121] a 14-item questionnaire, will be used to measure the degree to which women have found their lives to be unpredictable or uncontrollable within the past month. Items are scored from 0 to 4

	(0=never, 4=very often); higher scores reflect greater perceived stress.[122, 123] Cronbach α coefficients range between .84 and .86, as well as construct validity.[121, 122]
PSQI	Pittsburgh Sleep Quality Index.[124] The Pittsburgh Sleep Quality Index (PSQI) is well established measure of the quality and patterns of sleep in the older adult. Scoring is based on a 0 to 3 Likert scale with higher scores reflecting poorer sleep quality. The reliability coefficient of 0.83 is reported for its seven components. This instrument found that patients with HIV have poor sleep quality which influenced cognitive performance in HIV infected persons.[123]
HRQoL	The Medical Outcomes Study HIV Health Survey (MOS-HIV)[125, 126] which is a brief, comprehensive measure of health-related quality of life (HRQoL) used extensively in PLWH and AIDS will be given. The 35-item questionnaire includes ten dimensions (health perceptions, pain, physical, role, social and cognitive functioning, mental health, energy, health distress and quality of life (QoL) and takes approximately 5 minutes to complete. Subscales are scored on a 0-100 scale (a higher score indicates better health) and physical and mental health summary scores can be generated. The MOS-HIV has been shown to be internally consistent, correlate with concurrent measures of health, discriminate between distinct groups, predict future outcomes and be responsive to changes over time.[126]
AGAS	Antiretorival General Adherence Scale. Well validated and widely used measure of HIV medication adherence in persons with HIV.
ACTG HIV Symptoms	AIDS Clinical Trials Group HIV Symptoms. Widely used and validated measure to evaluate symptomology in persons with HIV.
Substance use and abuse questions	Will evaluate using brief questionnaire substance use and abuse history.
PROMIS	Patient Reported Outcomes Measurement Information System. (Emotional Support, Informational Support, Applied Cognitive Abilities, Fatigue, Pain Interference, Sleep Disturbance, Instrumental Support). A system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being.
Internalized HIV/AIDS Stigma	Internalized HIV/AIDS Stigma Scale
Exercise self-efficacy	Exercise Self-Efficacy Scale
Physical Activity Motivation Scale	Physical Activity Motivation Scale
Outcome expectancies for exercise scale	Outcome Expectations for Exercise Scale
Medical Outcomes Study-HIV	General health, wellbeing and activities questions
Heart Disease Fact Questionnaire	Knowledge of heart disease
VACS	(collected from patient medical records and entered into the Veterans Aging Cohort Study website). Age,
Functional status	Instrumental Activities of Daily Living Scale
HIV disclosure	HIV Disclosure Self-Report Questionnaire

Intervention and theoretical process variables will be evaluated using the measures below. We will measure exercise self-efficacy and the outcome of exercise self-efficacy scales at **Baseline, T1, T2 and T3** only. The other measures will be used to determine exercise prescription, participation and adherence to exercise.

Table 7. Theoretical and Intervention Process Measures

Measures	Description
Exercise Adherence	Average weekly adherence rates will be calculated as follows: (number of exercise sessions recorded/number of sessions prescribed) × 100. A total summary adherence score will be calculated by summing and dividing weekly adherence scores by total number of weeks walked. Data will be collected by downloading results from Fitbit.com and Fitabase, a comprehensive data management platform designed to support activity tracking devices.
Step Counts	Step counts will be indirectly assessed using the Omron HJ-7201ITC pedometer to count daily steps which can be downloaded to study computer at designated intervals; instructions on use and stride length will be taken during first CR visit. Omron pedometers have been shown to be accurate and reliable in adults,[127-129] patients with and more valid than measurement by questionnaire.[128, 130] Participants will be considered 100% adherent if they walk 5 times per week for 30 minute durations at 60 to 70% intensity level.

Step Calendar	To document exercise adherence, participants will be asked to record on a step calendar: maximum HR, highest rate of perceived exertion (RPE)[131] during walk, and number of steps walked during the walking sessions. In our previous studies, low literacy and persons with mild cognitive impairment were able to complete without difficulty.[46, 70, 71]
RPE	The 15 point (6-20) Borg Rate of Perceived Exertion (RPE) Scale[131] is a well established, valid measure of exertion and will be used to measure participants' subjective perception of effort.
Target HR	Target heart range (THR) will be used to monitor the intensity and training response to walking. Target exercise rate will equal peak HR established from CPET (Peak HR) X (0.60 to 0.70). Polar Beat ® Watch (FT 80) will be used to monitor intensity and duration for the aerobic training. The reliability and validity of Polar HR watches are well established.[132, 133] HR monitor and instructions on how to use it will be provided during the first home visit.
Exercise Self-Efficacy	The 18 item Exercise Self-Efficacy scale[134] will be adapted to measure exercise self-efficacy. It has shown strong psychometric properties, with an internal consistency of .90 or higher.[135-137] Scores range from 0 to 100 with higher scores reflecting greater self-efficacy.
OEE	The Outcome Expectations for Exercise Scale (OEE),[138] a 9 item scale, with established validity and reliability in older adults and African American's will be used to measure outcome expectations.
Six Minute Walk Test	A noninvasive test that at the first visit is done to get a baseline of how far the participant can walk and then administered at follow up visits to observe if any improvement is being made once the intervention is initiated.
Hand Grip Test	Administered with a dynamometer, this test is used for testing hand grip strength. This test provides a general index of a person's overall body strength. Tests are performed on both the left and right arms.

Quality and fidelity. Protocol manuals and scripts will be developed for the research visits and group sessions to maintain consistency and fidelity of the intervention content delivered. We will also use quality measures to document receipt of each component of the intervention by the research staff. All intervention staff will receive extensive training for exercise intervention (Dr. Gary). Research staff will also receive extensive training for conducting MI by a certified MI trainer (Dr. Holstad). Co-PI's will attend or monitor 20% of research and group sessions in the first year to track intervention adherence and quality checklists will be completed by research staff for the intervention and AC protocols. We will audio-tape all MI group sessions with permission and 20% will be randomly checked for fidelity to protocol by a non-study MI certified counselor. In addition, to maintain the accuracy of the results for the treadmill test, FMD, PWV or neurocognitive tests, research participants may be asked to take a urine drug screen to observe the use of COC (cocaine), THC (marijuana), OPI (opiates), AMP (amphetamine), and mAMP (*meth*-amphetamine) prior to these tests being administered. Individuals who use these types of drugs can alter the outcome and results of these tests. To obtain more accurate results, screening for these drugs would be beneficial. Furthermore, blood alcohol concentration (BAC) could also muddle the outcomes and results of these tests (treadmill, FMD, PWV, or neurocognitive), therefore research participants may also be asked to take an alcohol breathalyzer test. Participants will also be asked to download and /or create an account with Fitbit (if they are provided with a Fitbit). Participants will be monitored up to a year to observe objectively the number of steps they take, their HR, duration of exercise and elevated HR

Risks/Discomforts. Potential Risks are expected to be minimal since participants will be referred from and/or attending health clinics under the care of an infectious disease physician and receiving optimal medication therapies for HIV. We will conduct a brief history and physical examination before aerobic capacity tests (modified Balke or Bruce) are conducted. If a participant becomes fatigued and does not wish to continue, they will be rescheduled for an additional appointment to complete the remainder of the tests.

The risks associated with administering the modified Balke or Bruce treadmill tests are anticipated to be minimal but may include: atrial and ventricular arrhythmias, sudden death, angina, adverse blood pressure changes (high or low), dyspnea, fatigue, falling, orthopedic/musculoskeletal injuries and complaints, dizziness, and electrocardiographic evidence of ischemia. We will administer the modified Balke or Bruce, a symptom limited treadmill test, at the Clinical Research Network (CRN) by an exercise physiologist and under the supervision of a trained health care provider. Before the exercise testing, each participant will walk for 2 minutes to warm up and to avoid potential muscle soreness. Emergency equipment, medical and nursing staff are immediately available should the participant have any adverse response. A continuous electrocardiogram and blood pressure readings every 1 minute will be recorded. If ST elevation or multiple ventricular ectopy

occur the treadmill test will be stopped immediately. The participant will be continuously monitored during the treadmill test and VS taken every 1 minute for 5 minutes after the test, then every 5 minutes. If there are any untoward vital sign changes such as lower or higher BP, arrhythmia, chest pain or dizziness the study cardiologist (Dr. Quyyumi) will be notified. In our previous and ongoing work with heart failure patients, there were no untoward adverse events during the treadmill tests. Data from the HF-ACTION study[214] provides evidence of the safety of symptom limited exercise tests. Of the 4,411 symptom-limited exercise tests during 5 years, no deaths and only 2 nonfatal, major CV events occurred (0.45 events/1,000 tests). There were also no test-related events requiring hospitalization. It was concluded that in NYHA class II-IV patients with severe left ventricular systolic dysfunction, that symptom-limited exercise testing is safe based on no deaths and a rate of nonfatal major CV events that is <0.5 per 1,000 tests[150] Although participants in the current study will have CVD risks, they are not considered at heightened risk for adverse cardiovascular events during the treadmill test.

The potential risks associated with the Let's Move intervention are anticipated to be minimal. Any potential cardiovascular (CV) events that poses risk to the participant is anticipated to be detected during the modified Balke or Bruce maximal treadmill test. In addition, the duration of walking will be limited to 30 minutes during the first 2 weeks and at an intensity level (60%) that is not likely to result in any adverse CV events; if necessary participants can rest as needed until the 30 minute duration of walking is completed. Participants will wear a Polar HR monitor or a Fitbit so that HR and intensity level can be closely monitored. Participants in the study will be provided with detailed instructions on self-monitoring HR, BP and symptoms associated before, during and after walking. Each participant will be provided with a target heart rate range to stay within during the study period. Participants will be instructed to wear the Polar HR monitor or Fitbit during each exercise session. The participants will take their HR, and BP (if machine available) and weight prior to and after each walking session and record it in their walking calendar. Participants will be instructed to call the research staff if their BP or HR is outside their normal range. If participants are symptomatic, experience increased shortness of breath over the previous 24 hours, they will be instructed not to exercise. The participants will be instructed to take their medications as usual prior to exercise and instructed on proper attire for exercising. Demonstrations and return demonstrations of the Polar HR monitor or Fitbit will ensure they know how to wear the monitors (Polar HR monitors specifically around the chest) as well as trouble shoot when either of the monitors does not display correctly. They will be instructed that if their HR approaches within 5-10 beats of the target HR range to slow the walking pace down. In addition, they will be instructed to monitor their RPE using the Borg 6 to 20 scale, and to keep their RPE at 12-13 during the initial weeks and to gradually progress with instructions to 15 as stipulated in the protocol. Participants in the intervention groups will be advised to carry a cell phone when they walk at home in the event of an emergency or sudden event. Specifically, participants will be instructed to slow their pace if their HR increases to near THR as previously noted or if they become short of breath. Participants who have ischemic heart disease and prescribed nitroglycerin (NTG) will be instructed to carry their NTG with them during each walking sessions. If chest pain occurs during exercise, the participants will be told to stop exercising and to take a NTG as directed by their cardiologist. The participant will also be instructed if the chest pain continues to sit down and to call a relative or friend and to take another NTG if the chest pain does not subside. If the chest pain continues and is not relieved by NTG within 10 minutes they will be instructed to call 911. If the participant becomes moderately to severely dyspneic where they cannot talk while walking they will be instructed to stop walking until the dyspnea subsides. If the dyspnea continues once they have stopped walking for several minutes they will be instructed to call a relative or friend; if not dissipated they will be instructed to go the nearest emergency room. If a participant becomes dizzy while walking they will be asked to sit down and to get up slowly once the dizziness passes. In our previous and ongoing work with heart failure patients and family caregivers, there were no adverse events reported for walking at the 60-70% intensity levels using a very similar protocol. If symptoms are present at current intensity level or duration of walking the participant will not be progressed until exercising at current level with RPE at 15 or below for 45 minutes. This will better ensure the participant is not progressed too rapidly.

The *potential risk to participants in the control stretching/flexibility, 'Let's Flex'* movement group is anticipated to be minimal. Participants will be taught how to use stretching and flexibility movements by a research staff who is not involved with the intervention groups. In our previous and ongoing work with heart

failure and family caregivers, participants enjoyed this placebo exercise, but it was not strong enough to influence cardiovascular or biological outcomes. Although some participants did experience a better QOL from contact with the research team but this was not as strong as the intervention, and it was sustained for a shorter duration.

Potential risks related to *questionnaire completion* include the possibility of distress after the instrument administration or teaching session. Based on the preliminary work and patient responses to these types of questionnaires and interventions, we anticipate this risk to be minimal. The intervention should not increase distress over usual care. We also observed no increase in patient depressive symptom scores over time in other studies suggesting that the intervention did not introduce greater distress. However, if participants do indicate significant symptoms of depression by their responses on the BDI-II, mental health referral information will be provided and they will be asked if they would like a research team member to assist them in setting up a mental health referral. If at any time a participant indicates serious depressive symptoms or an intent to hurt him or herself, a family member will be informed (as agreed in the Informed Consent form) and/or their primary care provider alerted (again as agreed to in the Informed Consent). Other risks that occur are increased burden of participating in the intervention or attention control follow up calls and clinic visits. Distress after disclosure or awareness of drug and alcohol use. The blood sample will be collected by a research staff or laboratory assistant in the Clinical Research Network at each time point. The needles and syringes will be disposed in appropriate biohazard containers. The blood samples will be labeled by participant identification number, time point and stored in the research laboratory at -80 degrees until analyzed using the recommended ELISA procedures by the manufacturer. All laboratory specimens will be run twice to ensure reliability of blood tests. Slight bruising at the site of the venipuncture is possible. For any participants on anticoagulant therapy, additional pressure to site will be applied.

The study was designed to <u>minimize and protect against potential risks</u> by careful training of staff, emphasis on confidentiality, and efforts to increase convenience to the subject for each study activity. To reduce anxiety and emotional responses to the intervention, we will address these concerns as part of the sessions. In the rare event that subjects experience emotional distress, they will be referred to their provider, a clinical psychologist or clinical nurse specialist available to HIV patients. The total PHQ-2 will be reviewed as part of screening and those with severe depressive symptoms will be excluded. If PHQ-2 scores reveal that moderate depression (PHQ-2 > 4) is present, the participant will be informed and given information about local mental health resources and encouraged to contact their primary healthcare provider.

All patient records will be kept in a locked file cabinet in the research office and will be accessible only to the PI and the research team. All data will be coded by subject identification number, and no identifying information will be recorded on the data collection forms. The master list that will connect the codes to identifying information will be secured in the research project office. All data maintained in the computerized database will be accessible only with a login and protected, encrypted password. After the study is completed, all data will be kept according to regulations in a locked file.

The <u>potential risks to subjects are anticipated to be minimal, and the anticipated benefits</u> to patients enrolled in the study are potentially high. The majority of those who participate in aerobic exercise are expected to show an improvement in cognitive function, physiological status, aerobic capacity and QOL. Because CI and physical inactivity contributes to physical function decline and poor clinical outcomes in persons with HIV, improvement of physical function has the potential to significantly reduce the burden associated with this disorder and has potentially cost savings benefits. Based on our previous experience, we anticipate that the Let's Flex group may have an improvement in psychological functioning and QOL as a result of the contact with the research team members, but it will likely be of shorter duration than the intervention groups, and have no benefit on any of the other outcome variables. In addition, potentially Let's Flex participants may improve in HIV self-care behaviors based on the additional knowledge and education provided in the education sessions.

The <u>potential knowledge to be gained</u> from this study include a better understanding of the underlying mechanisms that contribute to CI and the influence of an aerobic exercise program on cognition, aerobic capacity and novel biomarkers. Moreover, testing a home-based intervention may increase future scalability and uptake of the intervention if efficacious.

6. Participant Selection

Eligibility criteria: Inclusion criteria include: (a) men and women aged 50 to 89 who are diagnosed with HIV/AIDS and willing to participate; (b) Native English speaking; (c) live independently and within a 30-45 mile radius of Atlanta; (d) not involved in any structured exercise program or exercising 3 or more times per week for a minimum of 30 minutes; (e) not involved in any weight loss program (f) not hospitalized within the last 60-days; (g) clinically stable and on ART 6 months before enrollment; (h) if on statins medication they are stable for 3 months; (i) score 3 or less on the verbal memory subtest of the MoCA; or (j) < 0.5 SD below mean on the Oral Trail Making Test B; (k) able to provide informed consent and pass a consent post-test. Exclusion: (a) non sedentary (defined as engaging in ≥ 30 minutes of moderately strenuous exercise 3 times or more a week); (b) medical or physical condition that would preclude participation in the exercise component of the study (e.g., severe arthritis or mobility problems, lower extremity amputations, joint replacement(s), balance disorders, dizziness, DOE with moderate exertion, difficulty walking one block, recent falls, obvious injury to lower extremity, uncontrolled hypertension or diabetes, renal failure, blindness, or a history of angina with activity); (c) ischemic changes or inappropriate BP changes on BL exercise (modified Balke or Bruce) treadmill test; (d) on oral corticosteroids (nasal, optical and inhaler corticosteroids allowed without restriction) , experiencing acute inflammation at time of baseline or follow-up testing (this will result in rescheduling of testing if no other exclusion criteria apply after 2 weeks); (e) presence of current opportunistic infection; (f) any terminal illness; (g) regular use of anti-inflammatory medications such as non-steroidal anti-inflammatory agents excluding low dose aspirin; (h) on anti-psychotics; (i) on tricyclic antidepressants; (j) on anti-depressants equal to the equivalent of more than 1 mg of Clonazepam; (k) on Lithium; (l) women who are pregnant; (m) severe learning disabilities, intellectual disabilities, schizophrenia, bipolar, psychotic disorders to minimize confounding effects on neurocognitive data; (n) confounding neuro-medical conditions (e.g., active CNS opportunistic infections, seizure disorders, head injury with loss of consciousness greater than 30 minutes, intracranial neoplasms, stroke with neurological or neuropsychiatric sequelae, and non-HIV-associated dementias); (o) due to the high prevalence of Substance Use, Major Depressive and Generalized Anxiety Disorders in HIV disease[89] individuals with histories of these three conditions will *not* be excluded; however, we *will* exclude individuals who meet criteria for any Substance Use Disorder or Major Depression *within 6 months of evaluation (see Screening Interview below)*; (p) creatinine > 2.5 within the past 6 months; (q) PHQ-2 score ≥ 4; (r) completed 8 years or less of school (s) failed to pass post-consent test after three attempts; (t) two or more positive drug screen tests (also PI discretion); (u) alcohol breathalyzer test result ≥ 0.03; (v) PI discretion to withdraw research participants if the participant fails to maintain minimum research requirements. PI discretion for any inclusion or exclusion criteria listed above. Participants will be also recruited to ensure comparability across groups on demographic characteristics known to influence neuropsychological performance, including age, education, sex, ethnicity, and estimated premorbid Verbal IQ (using the American National Adult Reading Test-AMNART).[90] The sample inclusion/ exclusion criteria were selected to eliminate conditions that would confound the dependent variables or interfere with participation in the interventions.

Recruitment and enrollment will occur through posted flyers in the recruiting clinics, through physician and nurse referral at the collaborating outpatient clinics. To facilitate referrals, study purpose and procedures will be discussed at clinical meetings, clinical and grand rounds, posted on research web sites, and during individual conferences with HIV providers at each of the enrolling sites by the investigative team. We will also arrange for regular recruitment events at the local recruitment clinics to distribute flyers and information about the study. There are also numerous support groups provided by the recruiting facilities and with permission we will distribute flyers and information about the study at those sessions. These strategies have been successful in our former and current studies. Potential participants may also be identified clinics and their medical records reviewed and contacted via research study recruitment letter.[46, 70, 72]

The initial recruitment letter has an alphanumeric code which is a unique, randomly generated identifier that will be attached to a recruitment letter sent to each participant in the study. The identifier is structured (M-AA-##-AA) with the first letter indicating the recruitment site. The participants who receive a recruitment letter will be informed about the research study as well as given instructions to go online to a designated secure

website to accept or decline entrance into the study. Those that reply will be asked to enter their unique code ID#, DOB, and current phone number and select yes to be contacted or no to be removed from contact list. Of the participants that reply with interest in inclusion, within 3 business days research staff will contact them via the phone number given. Those that do not respond at all will receive a call within 1-2 weeks from a member of the research staff to verify interest. This information is stored on a secured server at the Emory School of Nursing, and any information obtained will only be used for the strict purpose of the approved study design. The subsequent recruitment letter will not contain the unique alphanumeric code, however the letter will still contain information about the study and staff contact information. Similar to before, those that do not respond will receive a call within 1-2 weeks from a member of the research staff to verify interest. Recruitment letters being mailed to clinic patients will also be accompanied by a letter from the clinic staff declaring the collaboration between the clinic and the research team elevating any apprehension to legitimacy of the research and patient confidentiality.

In addition, Dr. Waldrop-Valverde is PI of an ongoing study of adults living with HIV/AIDS called Project READ. READ includes patients from the same clinics proposed for recruitment/enrollment for this study – FiT BRAiN. As part of the informed consent process of project READ, participants can indicate if they are willing to be contacted for their interest in future studies led by the PI. For those persons who have indicated "yes" to this question and who are 50 years old or older, we will telephone them (based on their last known phone number) to inform them about the study and gauge their interest. If interested, the same screening procedures will take place.

Screening and Enrollment: The Project Coordinator or Recruiter will communicate biweekly with the clinic staff to remind them to refer potential HIV patients to be seen in the enrolling sites. Those interested and referred will be **Pre-Screened** either by phone or in person. Part of the pre-screen will provide verbal informed consent and then complete a Pre-Screening Interview. To rule out severe cognitive impairment or possible dementia that may interfere with study participation, the Montreal Cognitive Assessment (MoCA) memory subtest will be given. Those who score ≤ 3 on the MoCA will be eligible. In addition, the Oral Trail Making Test B will also be given. Those with < 0.5 SD will be eligible. Finally participants will asked "Have you been diagnosed with Major Depressive Disorder, Substance Use Disorder, or Anxiety Disorder in the past 6 months?" to rule out Substance Dependence and Major Depression in the previous 6 months. Those meeting the criteria for eligibility will be enrolled to the full study and scheduled for baseline

7. Statistical Analysis.

Phase 3 Data Analysis. The objectives of phase 3 are to: 1) maintain data files; 2) evaluate study outcomes; and 3) disseminate study results and project materials.

Data management Procedures for data management and monitoring will be initiated during the start-up phase. The project coordinator will coordinate the organization and processing of forms, and schedule and implement checks of data quality and completeness. Data from the ACASI files will be saved in the database. Data will be backed up on a regular basis to prevent loss of data. Data will be transferred electronically from the sites to a secure password protected network drives where it will be checked and downloaded. A data-checking plan based on each questionnaire will be used to look for suspicious entries. Data monitoring will include scheduled checks for completeness every 2-4 weeks. Data sets from all assessment points will be merged as necessary to answer the research questions. Dr. Guo will oversee the final quality assurance/quality control data reviews. She will design and conduct the statistical analyses; assist as needed with designing research forms and data entry; and collaborate with the investigators on analysis and interpretation. We have successfully used these procedures in our research projects.

Sample size and Power Calculation. For longitudinal analyses of cognitive functioning and biological measures (Aims 1 and 2), our sample size provides adequate power (80%) to detect effect sizes of 0.37 or larger at alpha=0.05. Our ongoing study (Caregiver Stress study) showed that between-group effect sizes related to exercise vs. AC groups are on the order of 0.5 to 0.8 for physiological, physical and psychological functions.

Additionally, a study for older adults with mild cognitive impairment[139] showed effect sizes related to exercise vs. stretching groups on the order of 0.4 to 0.6 for cognitive functioning and other biomarkers. Assuming the expected effect size related to exercise in our study is similar to that observed in the previous studies, the proposed sample size will provide adequate power to detect relatively small between group differences between our exercise and AC groups. For mediation analysis in Aim 3, the proposed sample size can provide 80% power to detect effect size of 0.39 or larger for the mediation effect of the biomarkers on the relation between exercise and cognitive function. Therefore, the sample size will provide adequate power to detect medium effect sizes[93] for the mediation analysis in Aim 3.

Statistical Analyses. General Considerations in Statistical Analyses: Our initial data exploration will include: 1) determining the distributions of outcome measures and assessing whether data transformations are needed, 2) insuring that the underlying assumptions of statistical analyses are satisfied, 3) identifying potential co-linearity problems, and 4) identifying potential outliers that require further investigation. For categorical variables, we will check for sparse cells and regroup categories if necessary. In building statistical models, we will check linearity assumptions for continuous predictors and consider higher-order terms if needed. *Missing Data*. We will make every effort to minimize missing data by monitoring the degree of missing data regularly and implementing successful methods for obtaining follow-up data. When data cannot be collected, sensitivity analysis will be performed to evaluate the impact of missing data on results. We also plan to use restricted maximum likelihood (REML) method for estimating the longitudinal statistical models to minimize the impact of missing data. This will make it possible to retain cases with partial data while making less restrictive assumptions about missing data patterns. *Controlling for Confounding*. Our analyses will account for potential confounding factors such as medications, gender, BMI and other specific confounders for each aim. *Adjustment for stratification variables*. We plan to adjust for the stratification variable, i.e. study site, in the statistical analysis. This will correct for correlation between the treatment groups due to the balanced randomization within each site and consequently provide better statistical power in detecting differences between treatment groups.[140] *Adjustment for Multiple Measures and Comparisons.* We will apply adjustments such as Bonferroni correction when appropriate to adjust for multiple comparisons. A combination of statistical software will be used for statistical analysis and data visualization, including SPSS (v.20), SAS (v. 9.3), and R (v. 3.0.1). All statistical tests will be two-sided and intent-to-treat procedures will be employed.

AIM 1. Neurocognitive Improvement: We expect the primary cognitive improvements to be found in executive skill, episodic memory, and processing speed (as measured by CANTAB) since these skills are most susceptible to the effects of exercise. As recommended by Grant and Marcotte,[141] demographically adjusted scores will be used to test for intervention effects between the treatment and attention control conditions over the study time period. To adjust for the effects of practice from repeated testing, we develop z-scores for each of the neuropsychological assessment tests using the regression-based method.[142] Specifically, we first use multiple regression from control participants' test scores to derive the norms for change across visit times. Then we calculate the z-score by adjusting the raw test score with the expected normal follow-up score based on the subject's baseline characteristics using the multiple regression model. This method accounts not only for the effects of practice but also test-retest reliability (e.g., regression to the mean, ceiling and floor effects) and is the method suggested for use with clinical samples.[142] The z-scores will be used as the outcome measures in the following statistical analyses. We will then use the confidence-interval-based method[143] to classify whether a subject has shown improved cognitive functioning when comparing to the norms for change.[144] Specifically, we will define "no change" on each cognitive test using a 90% confidence interval (CI) based on the norms generated from the control subjects' data. Then, participants who score above the upper bound of the 90% CI, i.e. in the top 5% of the normal distribution , will be defined as "improved", while those within the 90% CI defined as "no change" and those below the lower bound of the CI defined as "decliners".
Modeling and Hypothesis testing. Repeated measures analysis will be performed to model the z-scores of the NP tests, the classified improvement status and other outcome measures longitudinally to test whether there are differences between the two intervention groups in terms of executive skill, episodic memory and information processing speed at T1 and T3 assessments. Specifically, multilevel models including linear mixed models

(LMM: for continuous outcomes) and generalized linear mixed models (GLMM: for categorical outcomes) will be implemented using SAS (version 9.3; SAS Institute, Cary, NC) where each subject is treated as an experimental unit in the mixed model. An unstructured variance–covariance form will be assumed in repeated measurements within a subject, which provides the most flexible modeling of the covariance structure. Predictors in the models will include 1) visit time 2) intervention group, 3) interaction term between visit time and intervention group and 4) potential confounding factors such as nadir CD4 count, the CPE score (CNS penetration effectiveness of the antiretroviral regimen), ART adherence, time since diagnosis, estimated premorbid IQ, and HAND diagnosis. The fitted mixed model will provide model-based estimates and tests for the outcome measures for the two intervention groups at each time point of the study. Hypotheses tests based on specific contrasts in the mixed model and the interaction term between visit time and intervention group will be performed to test the hypotheses that subjects in the Let's Move program demonstrated improved cognitive functioning as compared to Let's Flex control group.

AIM 2. Repeated measures analysis using multilevel models will be performed to test whether there are differences between the two intervention groups in terms of the inflammatory biomarkers, endothelial vascular function and neuronal growth biomarker at T1 and T3 assessments. Prior to fitting the multilevel models, the distributions of the biomarkers will be checked and appropriate transformations will be performed for skewed biomarkers. Similar strategies as in Aim 1 will be used to construct the multilevel models and to perform model-based tests to evaluate the hypotheses in Aim 2.

AIM 3. To assess whether the association between the Let's Move program and cognitive function may be potentially or partially mediated by inflammatory biomarkers, BDNF and endothelial vascular function, we will first apply the standard regression-based approach[145, 146] in which several regression analyses are conducted and significance of the coefficients is examined at each step to evaluate the mediation effects. Furthermore, we plan to apply a cross-lagged panel model (CLPM)[147] for longitudinal data to test the mediation effects of the biomarkers at T1 and T3 assessments. The CLPM is a multivariate model based on structural equation modeling (SEM) for testing mediational processes in longitudinal designs. Compared to cross-sectional mediation methods, the CLPM accounts for lagged effects in testing mediation hypotheses in longitudinal data, supports stronger inference about the direction of causation in comparison to models using cross-sectional data, and can reduce the probable parameter bias that arises when using cross-sectional data.

8. Adverse Event Reporting.

As outlined in the DSMP below, the IRB will be notified of reportable events within one week of the event by the study PIs. Adverse events will also be reported to the NINR Program Officer within one week of the event.

9. Data Safety and Monitoring Plan (DSMP)

A safety monitoring committee (SMC) will be established to monitor the study. This committee will be composed of:

Chair: **Dr. Sandra Dunbar,** RN, PhD, Professor, Associate Dean for Academic Advancement, School of Nursing, Emory University

Members: **Elizabeth Corwin,** Rn, PhD, Professor, Associate Dean for Research, School of Nursing, Emory University

Sudeshna Paul, PhD, Assistant Professor, Biostatistics, School of Nursing, Emory University

The SMC will meet with the PIs **annually** or as needed to review conduct of the trial, including informed consent procedures, accrual, recruitment, and retention, violations in protocols, adverse events, breaches in confidentiality, or other data related to the protection of human subjects. They will also review and make

recommendations on the data transfer and warehousing procedures. The primary role of the SMC will be to ensure data integrity and the safety of participants. They will have the power to recommend conclusion of the trial and provision of the intervention to the control group if significant improvements in outcomes occur. They will also have the power to recommend conclusion of the trial if significant risks develop, or if the project is unlikely to conclude successfully.

The first meeting will occur at the beginning of the trial and at this meeting the committee will review and make recommendations about the consent procedures, and situations within which confidentiality may be broken, such as if a participant becomes a threat of physical harm to self or others. In addition, study protocols, recruitment, retention procedures will be examined for timeliness, practicality, safety, and protection of human subjects. Any recommendations that emanate from monitoring activities will be communicated to the NINR within 7 days if the human subjects research or DSM plan is changed prior to implementation of the trial for approval prior to initiation.

At the subsequent regular annual meetings, the SMC will review:

a. adherence to the goals for recruitment and retention;
b. adherence to the study protocols;
c. cumulative data for evidence of study related adverse events;
d. quality, completeness, and timeliness of the data collected;
e. factors that could affect the outcome or compromise participant/data confidentiality;
f. other factors outside the study (e.g., therapeutic developments, agency related policies) that could impact the safety of participants or the ethical conduct of the study.

In general, recommendations the SMC may make include:

a. continue the study without change;
b. modifications to the study protocol;
c. suspension or early termination;
d. alternative approaches to consider (e.g., if there is a failure to accrue participants as anticipated).

All adverse events that occur during the study will be sent to the SMC chairperson, who will distribute them to the other members of the committee. The relatedness of the event to the study would be provided at the time of presentation of the information. In addition the Emory University IRB and the NINR Program Officer will be notified within one week of the event by the study PIs. The SMC chairperson will transmit an annual report of its findings to the funding agency, the local IRB, and the study PIs.

In compliance with the NINR DSM Policy on Extramural Clinical Trials 2014, the PIs will report the following to the NINR:

a. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol.
b. IRB-approved revisions to the study protocol that indicate a change in risk for participants.
c. A summary of recommendations made by the SMC and an action plan for response.
d. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

10. No pharmaceuticals, biologics, or devices are to be included in this study.

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